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(FILE 'HOME' ENTERED AT 14:55:13 ON 20 JAN 2008)

FILE 'REGISTRY' ENTERED AT 14:57:36 ON 20 JAN 2008

E METHOTREXATE/CN

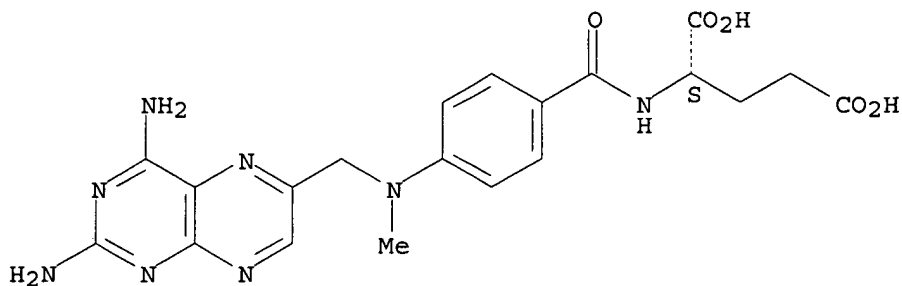
L1 1 S E3

FILE 'CAPLUS, MEDLINE' ENTERED AT 14:58:54 ON 20 JAN 2008

L2 40819 S L1  
L3 0 S L2 AND ?UROMAMIDE?  
L4 0 S L2 AND ?UROAMIDE?  
L5 2 S L2 AND ?URONAMIDE?  
L6 40817 S L2 NOT L5  
L7 3740 S L6 AND RHEUMATOID ARTHRITIS  
L8 2 S L7 AND A3AR  
L9 3738 S L7 NOT L8  
L10 14 S L9 AND ADENOSINE RECEPTOR?  
L11 187265 S HIS  
L12 3724 S L9 NOT L10  
L13 2583 S L12 AND PATIENT?  
L14 0 S L13 AND ?MECA  
L15 0 S L12 AND ?MECA  
L16 805 S L13 AND INFLAMM?  
L17 15 S L16 AND AGONIST?  
L18 0 S METHOTREXATE/TI (P) ?MECA/CN  
L19 0 S METHOTREXATE/TI (P) ?MECA/TI  
L20 4 S METHOTREXATE (P) ?MECA (P) RHEUMATOID ARTHRITIS  
L21 4 S METHOTREXATE (P) ?MECA (P) ARTHRITIS  
L22 0 S L20 NOT L21  
L23 109 S L16 AND ORAL?  
L24 16 S ?MECA (P) RHEUMATOID ARTHRITIS  
L25 0 S L23 AND ADENOSINE A3 RECEPTOR?  
L26 0 S L23 AND A3 RECEPTOR?  
L27 2 S L9 AND ADENOSINE A3 RECEPTOR?  
L28 3736 S L9 NOT L27  
L29 0 S L28 AND A3 RECEPTOR?  
L30 0 S L23 AND DOSEGE?  
L31 46 S L23 AND DOSAGE?

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2008 ACS on STN  
 RN 59-05-2 REGISTRY  
 ED Entered STN: 16 Nov 1984  
 CN L-Glutamic acid, N-[4-[(2,4-diamino-6-pteridiny)methyl]methylamino]benzo  
 yl]- (CA INDEX NAME)  
 OTHER CA INDEX NAMES:  
 CN Glutamic acid, N-[p-[(2,4-diamino-6-pteridiny)methyl]methylamino]benzoyl  
 ]-, L-(+)- (8CI)  
 OTHER NAMES:  
 CN (+)-Amethopterin  
 CN 4-Amino-10-methylfolic acid  
 CN 4-Amino-N10-methylfolic acid  
 CN 4-Amino-N10-methylpteroylglutamic acid  
 CN Amethopterin  
 CN Amethopterin  
 CN Antifolan  
 CN CL 14377  
 CN EMT 25299  
 CN Emtexate  
 CN L-Amethopterin  
 CN L-Methotrexate  
 CN Ledertrexate  
 CN Metatrexan  
 CN Methotrexat-Ebewe  
 CN Methotrexate  
 CN Methotrexate  
 CN Methoxtrexate  
 CN Methylaminopterin  
 CN Mexate  
 CN MTX  
 CN N-[p-[(2,4-Diamino-6-pteridiny)methyl]methylamino]benzoyl]-L-(+)-glutamic  
 acid  
 CN NSC 740  
 CN R 9985  
 CN Rheumatrex  
 CN Trexall  
 FS STEREOSEARCH  
 MF C20 H22 N8 O5  
 CI COM  
 LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOSIS,  
 BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST,  
 CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, HSDB\*, IFICDB, IFIPAT, IFIUDB,  
 IMSCOSEARCH, IPA, MEDLINE, MRCK\*, MSDS-OHS, PHAR, PROMT, PROUSDDR, PS,  
 RTECS\*, SCISEARCH, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2,  
 USPATFULL, USPATOLD, VETU  
 (\*File contains numerically searchable property data)  
 Other Sources: EINECS\*\*, NDSL\*\*, TSCA\*\*, WHO  
 (\*\*Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



**\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\***

14908 REFERENCES IN FILE CA (1907 TO DATE)

895 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

14947 REFERENCES IN FILE CAPLUS (1907 TO DATE)

73 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L5 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:666025 CAPLUS  
DOCUMENT NUMBER: 145:152690  
TITLE: Method for inducing crystalline state transition in  
pharmaceuticals  
INVENTOR(S): Nakamichi, Kouichi; Izumi, Shougo; Oka, Masaaki  
PATENT ASSIGNEE(S): Nippon Shinyaju Company, Ltd., Japan  
SOURCE: U.S., 18 pp., Cont.-in-part of U. S. 5,456,923.  
CODEN: USXXAM  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5811547	A	19980922	US 1995-416815	19950609
CA 2147279	A1	19940428	CA 1993-2147279	19931013
WO 9408561	A1	19940428	WO 1993-JP1469	19931013
W: AU, BR, CA, FI, HU, JP, KR, NO, NZ, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9351607	A	19940509	AU 1993-51607	19931013
EP 665009	A1	19950802	EP 1993-922625	19931013
EP 665009	B1	20000216		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 189770	T	20000315	AT 1993-922625	19931013
ES 2145063	T3	20000701	ES 1993-922625	19931013
US 5456923	A	19951010	US 1993-129133	19931115
PRIORITY APPLN. INFO.:			JP 1992-303085	A 19921014
			WO 1993-JP1469	W 19931013
			US 1993-129133	A2 19931115
			JP 1991-112554	A 19910416
			WO 1992-JP470	W 19920414

AB This invention has for its object to provide a method of inducing a transition in crystalline state of a crystallizable pharmaceutical with great ease and improved efficiency and uniformity on a high production scale. An extruder is used for inducing a transition from one crystalline state ( $\Delta$ ) to another crystalline state in a crystallizable pharmaceutical. An extruded indomethacin (form  $\alpha$ ) was converted to an amorphous form.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:2517 CAPLUS  
DOCUMENT NUMBER: 132:106828  
TITLE: Ligand-activation of the adenosine A2a receptors inhibits IL-12 production by human monocytes  
AUTHOR(S): Link, Amrey A.; Kino, Tomoshige; Worth, James A.; McGuire, Jennifer L.; Crane, Marianna L.; Chrousos, George P.; Wilder, Ronald L.; Elenkov, Ilia J.  
CORPORATE SOURCE: Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, 20892, USA  
SOURCE: Journal of Immunology (2000), 164(1), 436-442  
CODEN: JOIMA3; ISSN: 0022-1767  
PUBLISHER: American Association of Immunologists  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Adenosine (ADO) exerts potent anti-inflammatory and immunosuppressive effects. In this paper we address the possibility that these effects are partly mediated by inhibition of the secretion of IL-12, a proinflammatory cytokine and a major inducer of Th1 responses. We demonstrate that 5'-N-ethylcarboxamidoadenosine (NECA), a nonspecific ADO analog, and

2-p-(2-carbonylethyl)phenylethylamino-5'-N-ethylcarboxamidoadenosine (CGS-21680), a specific A2a receptor agonist, dose-dependently inhibited, in whole blood ex vivo and monocyte cultures, the production of human IL-12 induced by LPS and Staphylococcus aureus Cowan strain 1. However, the A1 receptor agonist 2-chloro-N6-cyclopentyladenosine and the A3 receptor agonists N6-benzyl-NECA and 1-deoxy-1-[6-[[[3-iodophenyl)methyl]amino]-9H-purin-9-yl]-N-methyl-β-D-ribofuranuronamide expressed only weak inhibitory effects. On the other hand, NECA and CGS-21680 dose-dependently potentiated the production of IL-10. The differential effect of these drugs on monocyte IL-12 and IL-10 production implies that these effects are mediated by A2a receptor signaling rather than by intracellular toxicity of ADO analog's metabolites. Moreover, CGS-21680 inhibited IL-12 production independently of endogenous IL-10 induction, because anti-IL-10 Abs failed to prevent its effect. The selective A2a antagonist 8-(3-chlorostyryl) caffeine prevented the inhibitory effect of CGS-21680 on IL-12 production. The phosphodiesterase inhibitor Ro 20-1724 dose-dependently potentiated the inhibitory effect of CGS-21680 and, furthermore, Rp-cAMPS, a protein kinase A inhibitor, reversed the inhibitory effect of CGS-21680, implicating a cAMP/protein kinase A pathway in its action. Thus, ligand activation of A2a receptors simultaneously inhibits IL-12 and stimulates IL-10 production by human monocytes. Through this mechanism, ADO released in excess during inflammatory and ischemic conditions, or tissue injury, may contribute to selective suppression of Th1 responses and cellular immunity.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:1231544 CAPLUS

DOCUMENT NUMBER: 146:55056

TITLE: Methotrexate enhances the anti-inflammatory effect of CF101 via up-regulation of the A3 adenosine receptor expression

AUTHOR(S): Ochaion, A.; Bar-Yehuda, S.; Cohn, S.; Del Valle, L.; Perez-Liz, G.; Madi, L.; Barer, F.; Farbstein, M.; Fishman-Furman, S.; Reitblat, T.; Reitblat, A.; Amital, H.; Levi, Y.; Molad, Y.; Mader, R.; Tishler, M.; Langevitz, P.; Zabutti, A.; Pnina, Fishman

CORPORATE SOURCE: Can-Fite Biopharma Ltd., Petah-Tikva, 49170, Israel

SOURCE: Arthritis Research & Therapy (2006), 8(6), No pp. given  
CODEN: ARTRCV; ISSN: 1478-6362  
URL: <http://arthritis-research.com/content/pdf/ar2078.pdf>

PUBLISHER: BioMed Central Ltd.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Methotrexate (MTX) exerts an anti-inflammatory effect via its metabolite adenosine which subsequently activates adenosine receptors. The A3 adenosine receptor (A3AR) was found to be highly expressed in inflammatory tissues and peripheral blood mononuclear cells (PBMNC) of adjuvant induced arthritis (AIA) rats. CF101 (IB-MECA), an A3AR agonist, was found earlier to inhibit the clin. and pathol. manifestations of AIA. The aim of the present study was to look at the effect of MTX on A3AR expression level and at the efficacy of the combined treatment of CF101 and MTX in AIA rats. AIA rats were treated with MTX, CF101 or MTX+CF101. A3AR mRNA, protein expression level and exhibition were tested in the paw and PBMNC exts. derived from AIA rats utilizing immunohistochem. staining, RT-PCR and Western blot anal. A3AR level was tested in PBMNC extract derived from chronically treated MTX patients vs. healthy subjects. The effect of CF101, MTX and the combined treatment on A3AR expression level was also tested in PHA stimulated PBMNC from healthy subjects and from MTX treated RA patients. Combined treatment of CF101 and MTX resulted in an additive anti-inflammatory effect in AIA rats. MTX induced A2AAR and A3AR over-expression in the paw cells from the treated animals. Moreover, an increase in A3AR expression level was detected in the PBMNC of MTX treated Rheumatoid arthritis (RA) patients vs, cells from healthy subjects. MTX also increased the protein expression level of PHA stimulated PBMNC from healthy subjects. The increase in A3AR level was counteracted in vitro by adenosine deaminase (ADA) and mimicked in vivo by Dipyridamole, demonstrating that receptor over-expression was mediated by adenosine. In conclusion, the data presented in this study indicate that MTX induces an increase in A3AR exhibition and expression thereby potentiating the inhibitory effect of CF101, supporting a combined use of these drugs to treat RA.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 2 MEDLINE on STN

ACCESSION NUMBER: 2007052342 MEDLINE

DOCUMENT NUMBER: PubMed ID: 17101059

TITLE: Methotrexate enhances the anti-inflammatory effect of CF101 via up-regulation of the A3 adenosine receptor expression.

AUTHOR: Ochaion Avivit; Bar-Yehuda Sara; Cohn Shira; Del Valle Luis; Perez-Liz Georginia; Madi Lea; Barer Faina; Farbstein Motti; Fishman-Furman Sari; Reitblat Tatiana; Reitblat Alexander; Amital Howard; Levi Yair; Molad Yair; Mader Reuven; Tishler Moshe; Langevitz Pnina; Zabutti Alexander; Fishman Pnina

CORPORATE SOURCE: Can-Fite Biopharma Ltd, 10 Bareket Street, Kiryat-Matalon,  
Petah-Tikva, 49170, Israel.  
SOURCE: Arthritis research & therapy, (2006) Vol. 8, No. 6, pp.  
R169.  
Journal code: 101154438. E-ISSN: 1478-6362.  
PUB. COUNTRY: England: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200702  
ENTRY DATE: Entered STN: 30 Jan 2007  
Last Updated on STN: 27 Feb 2007  
Entered Medline: 23 Feb 2007

AB Methotrexate (MTX) exerts an anti-inflammatory effect via its metabolite adenosine, which activates adenosine receptors. The A3 adenosine receptor (A3AR) was found to be highly expressed in inflammatory tissues and peripheral blood mononuclear cells (PBMCs) of rats with adjuvant-induced arthritis (AIA). CF101 (IB-MECA), an A3AR agonist, was previously found to inhibit the clinical and pathological manifestations of AIA. The aim of the present study was to examine the effect of MTX on A3AR expression level and the efficacy of combined treatment with CF101 and MTX in AIA rats. AIA rats were treated with MTX, CF101, or both agents combined. A3AR mRNA, protein expression and exhibition were tested in paw and PBMC extracts from AIA rats utilizing immunohistochemistry staining, RT-PCR and Western blot analysis. A3AR level was tested in PBMC extracts from patients chronically treated with MTX and healthy individuals. The effect of CF101, MTX and combined treatment on A3AR expression level was also tested in PHA-stimulated PBMCs from healthy individuals and from MTX-treated patients with rheumatoid arthritis (RA). Combined treatment with CF101 and MTX resulted in an additive anti-inflammatory effect in AIA rats. MTX induced A2AAR and A3AR over-expression in paw cells from treated animals. Moreover, increased A3AR expression level was detected in PBMCs from MTX-treated RA patients compared with cells from healthy individuals. MTX also increased the protein expression level of PHA-stimulated PBMCs from healthy individuals. The increase in A3AR level was counteracted in vitro by adenosine deaminase and mimicked in vivo by dipyridamole, demonstrating that receptor over-expression was mediated by adenosine. In conclusion, the data presented here indicate that MTX induces increased A3AR expression and exhibition, thereby potentiating the inhibitory effect of CF101 and supporting combined use of these drugs to treat RA.

ACCESSION NUMBER: 2002:822462 CAPLUS  
 DOCUMENT NUMBER: 138:265678  
 TITLE: Modulation of gene expression associated with inflammation, proliferation and neurite outgrowth using antisense and enzymic nucleic acid-based technologies  
 INVENTOR(S): Blatt, Lawrence; Chowrira, Bharat; Haeberli, Peter; McSwiggen, James; Fosnaugh, Kathy  
 PATENT ASSIGNEE(S): Ribozyme Pharmaceuticals, Incorporated, USA  
 SOURCE: PCT Int. Appl., 317 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 258  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081628	A2	20021017	WO 2002-XC10512	20020403
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 9851819	A	19980611	AU 1998-51819	19980112
AU 729657	B2	20010208		
AU 9939188	A	19990916	AU 1999-39188	19990713
AU 769175	B2	20040115	AU 2000-56616	20000911
US 2003113891	A1	20030619	US 2001-827395	20010405
US 2003119017	A1	20030626	US 2002-156306	20020528
US 7022828	B2	20060404		
US 2003143732	A1	20030731	US 2002-224005	20020820
US 2003148507	A1	20030807	US 2002-226992	20020823
US 2003191077	A1	20031009	US 2002-230006	20020828
AU 2006203062	A1	20060810	AU 2006-203062	20060713
AU 2006203725	A1	20060914	AU 2006-203725	20060825
AU 2006228026	A1	20061102	AU 2006-228026	20061011

## PRIORITY APPLN. INFO.:

US 2001-827395	A	20010405
US 2001-294412P	P	20010529
US 2001-315315P	P	20010828
AU 1995-26422	A3	19950518
US 1996-623891	A	19960325
AU 1996-76662	A3	19961025
US 2000-181797P	P	20000211
US 2001-780533	A2	20010209
AU 2003-216323	A3	20030220
AU 2003-219817	A3	20030220
AU 2003-221258	A3	20030220

AB The present invention relates to nucleic acid mols., including antisense, enzymic nucleic acid mols., and RNA interference mols., which modulate the expression of genes encoding prostaglandin D2 receptor, adenosine receptor A1, NOGO receptor, IκB protein kinase, and protein kinase PKR. Thus, nucleic acids encoding these products are scanned to identify targets for cleavage by designed enzymic nucleic acids, such as hammerhead ribozymes, Inozymes, Zinzymes, DNazymes, and Amberzymes. Chemical modifications in the sugar, base, and/or phosphate backbones of these enzymic nucleic acids is carried out to improve their stability. Inhibition of gene product expression may be used for treatment of



diseases associated with said expression. [This abstract record is one of four records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.]

L10 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:822460 CAPLUS

DOCUMENT NUMBER: 138:83412

TITLE: Modulation of gene expression associated with inflammation, proliferation and neurite outgrowth using antisense and enzymic nucleic acid-based technologies

INVENTOR(S): Blatt, Lawrence; Chowrira, Bharat; Haeberli, Peter; McSwiggen, James; Fosnaugh, Kathy

PATENT ASSIGNEE(S): Ribozyme Pharmaceuticals, Incorporated, USA

SOURCE: PCT Int. Appl., 317 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 258

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081628	A2	20021017	WO 2002-XB10512	20020403
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 9851819	A	19980611	AU 1998-51819	19980112
AU 729657	B2	20010208		
AU 9939188	A	19990916	AU 1999-39188	19990713
AU 769175	B2	20040115	AU 2000-56616	20000911
US 2003113891	A1	20030619	US 2001-827395	20010405
US 2003119017	A1	20030626	US 2002-156306	20020528
US 7022828	B2	20060404		
US 2003143732	A1	20030731	US 2002-224005	20020820
US 2003148507	A1	20030807	US 2002-226992	20020823
US 2003191077	A1	20031009	US 2002-230006	20020828
AU 2006203062	A1	20060810	AU 2006-203062	20060713
AU 2006203725	A1	20060914	AU 2006-203725	20060825
AU 2006228026	A1	20061102	AU 2006-228026	20061011
PRIORITY APPLN. INFO.:			US 2001-827395	A 20010405
			US 2001-294412P	P 20010529
			US 2001-315315P	P 20010828
			AU 1995-26422	A3 19950518
			US 1996-623891	A 19960325
			AU 1996-76662	A3 19961025
			US 2000-181797P	P 20000211
			US 2001-780533	A2 20010209
			AU 2003-216323	A3 20030220
			AU 2003-219817	A3 20030220
			AU 2003-221258	A3 20030220

AB The present invention relates to nucleic acid mols., including antisense, enzymic nucleic acid mols., and RNA interference mols., which modulate the expression of genes encoding prostaglandin D2 receptor, adenosine receptor A1, NOGO receptor, I $\kappa$ B protein kinase, and protein kinase PKR. Thus, nucleic acids encoding these products are scanned to identify targets for cleavage by designed enzymic nucleic acids, such as hammerhead ribozymes, Inozymes, Zinzymes, DNAzymes, and Amberzymes. Chemical

modifications in the sugar, base, and/or phosphate backbones of these enzymic nucleic acids is carried out to improve their stability. Inhibition of gene product expression may be used for treatment of diseases associated with said expression. [This abstract record is one of four records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L10 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:822456 CAPLUS

DOCUMENT NUMBER: 138:83411

TITLE: Modulation of gene expression associated with inflammation, proliferation and neurite outgrowth using antisense and enzymic nucleic acid-based technologies

INVENTOR(S): Blatt, Lawrence; Chowrira, Bharat; Haeberli, Peter; McSwiggen, James; Fosnaugh, Kathy

PATENT ASSIGNEE(S): Ribozyne Pharmaceuticals, Incorporated, USA

SOURCE: PCT Int. Appl., 317 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 258

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081628	A2	20021017	WO 2002-XA10512	20020403
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 9851819	A	19980611	AU 1998-51819	19980112
AU 729657	B2	20010208		
AU 9939188	A	19990916	AU 1999-39188	19990713
AU 769175	B2	20040115	AU 2000-56616	20000911
US 2003113891	A1	20030619	US 2001-827395	20010405
US 2003119017	A1	20030626	US 2002-156306	20020528
US 7022828	B2	20060404		
US 2003143732	A1	20030731	US 2002-224005	20020820
US 2003148507	A1	20030807	US 2002-226992	20020823
US 2003191077	A1	20031009	US 2002-230006	20020828
AU 2006203062	A1	20060810	AU 2006-203062	20060713
AU 2006203725	A1	20060914	AU 2006-203725	20060825
AU 2006228026	A1	20061102	AU 2006-228026	20061011
PRIORITY APPLN. INFO.:			US 2001-827395	A 20010405
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			AU 1995-26422	A3 19950518
			US 1996-623891	A 19960325
			AU 1996-76662	A3 19961025
			US 2000-181797P	P 20000211
			US 2001-780533	A2 20010209
			AU 2003-216323	A3 20030220
			AU 2003-219817	A3 20030220
			AU 2003-221258	A3 20030220

AB The present invention relates to nucleic acid mols., including antisense, enzymic nucleic acid mols., and RNA interference mols., which modulate the expression of genes encoding prostaglandin D2 receptor, adenosine receptor A1, NOGO receptor, IκB protein kinase, and protein

kinase PKR. Thus, nucleic acids encoding these products are scanned to identify targets for cleavage by designed enzymic nucleic acids, such as hammerhead ribozymes, Inozymes, Zinzymes, DNAzymes, and Amberzymes. Chemical modifications in the sugar, base, and/or phosphate backbones of these enzymic nucleic acids is carried out to improve their stability. Inhibition of gene product expression may be used for treatment of diseases associated with said expression. [This abstract record is one of 4 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L10 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:793747 CAPLUS

DOCUMENT NUMBER: 137:304816

TITLE: Modulation of gene expression associated with inflammation, proliferation and neurite outgrowth using antisense and enzymic nucleic acid-based technologies

INVENTOR(S): Blatt, Lawrence; Chowrira, Bharat; Haeberli, Peter; McSwiggen, James; Fosnaugh, Kathy

PATENT ASSIGNEE(S): Ribozyme Pharmaceuticals, Incorporated, USA

SOURCE: PCT Int. Appl., 317 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 258

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081628	A2	20021017	WO 2002-US10512	20020403
WO 2002081628	A3	20030220		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 9851819	A	19980611	AU 1998-51819	19980112
AU 729657	B2	20010208		
AU 9939188	A	19990916	AU 1999-39188	19990713
AU 769175	B2	20040115	AU 2000-56616	20000911
US 2003113891	A1	20030619	US 2001-827395	20010405
AU 2002307099	A1	20021021	AU 2002-307099	20020403
EP 1386004	A2	20040204	EP 2002-763926	20020403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003119017	A1	20030626	US 2002-156306	20020528
US 7022828	B2	20060404		
US 2005261212	A1	20051124	US 2002-206693	20020726
US 2003143732	A1	20030731	US 2002-224005	20020820
US 2003148507	A1	20030807	US 2002-226992	20020823
US 2003191077	A1	20031009	US 2002-230006	20020828
US 2003203870	A1	20031030	US 2003-430882	20030506
US 2005182008	A1	20050818	US 2004-923142	20040820
US 2007026394	A1	20070201	US 2004-471271	20041004
US 2006154271	A1	20060713	US 2005-255139	20051020
AU 2006203062	A1	20060810	AU 2006-203062	20060713
AU 2006203725	A1	20060914	AU 2006-203725	20060825
AU 2006228026	A1	20061102	AU 2006-228026	20061011
PRIORITY APPLN. INFO.:			US 2001-827395	A 20010405

US 2001-294412P	P 20010529
US 2001-315315P	P 20010828
AU 1995-26422	A3 19950518
US 1996-623891	A 19960325
AU 1996-76662	A3 19961025
US 2000-181797P	P 20000211
US 2001-780533	A2 20010209
WO 2001-US4273	A2 20010209
US 2001-292217P	P 20010518
US 2001-306883P	P 20010720
US 2001-311865P	P 20010813
US 2002-358580P	P 20020220
US 2002-362016P	P 20020306
US 2002-363124P	P 20020311
WO 2002-US10512	W 20020403
WO 2002-US15876	A2 20020520
US 2002-156306	A1 20020528
US 2002-386782P	P 20020606
AU 2003-216323	A3 20030220
AU 2003-219817	A3 20030220
AU 2003-221258	A3 20030220
WO 2003-US5028	A2 20030220
WO 2003-US5346	A2 20030220
US 2003-427160	A2 20030430
US 2003-430882	A2 20030506
US 2003-444853	A2 20030523
US 2003-693059	A2 20031023
US 2003-720448	A2 20031124
US 2003-727780	A2 20031203
US 2004-757803	A2 20040114
US 2004-543480P	P 20040210
US 2004-780447	A2 20040213
US 2004-826966	A2 20040416
WO 2004-US13456	A2 20040430
WO 2004-US16390	A2 20040524

AB The present invention relates to nucleic acid mols., including antisense, enzymic nucleic acid mols., and RNA interference mols., which modulate the expression of genes encoding prostaglandin D2 receptor, adenosine receptor A1, NOGO receptor, I $\kappa$ B protein kinase, and protein kinase PKR. Thus, nucleic acids encoding these products are scanned to identify targets for cleavage by designed enzymic nucleic acids, such as hammerhead ribozymes, Inozymes, Zinzymes, DNAzymes, and Amberzymes. Chemical modifications in the sugar, base, and/or phosphate backbones of these enzymic nucleic acids is carried out to improve their stability. Inhibition of gene product expression may be used for treatment of diseases associated with said expression. [This abstract record is one of four records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L10 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:235649 CAPLUS

DOCUMENT NUMBER: 133:99286

TITLE: Reversal of the antiinflammatory effects of methotrexate by the nonselective adenosine receptor antagonists theophylline and caffeine: evidence that the antiinflammatory effects of methotrexate are mediated via multiple adenosine receptors in rat adjuvant arthritis

AUTHOR(S): Montesinos, M. Carmen; Yap, Josephine S.; Desai, Avani; Posadas, Inmaculada; McCrary, Christine T.; Cronstein, Bruce N.

CORPORATE SOURCE: New York University Medical Center, New York, NY, 10016, USA

SOURCE: Arthritis & Rheumatism (2000), 43(3), 656-663  
CODEN: ARHEAW; ISSN: 0004-3591  
PUBLISHER: Lippincott Williams & Wilkins  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Weekly low-dose methotrexate (MTX) remains the mainstay of 2nd-line therapy for rheumatoid arthritis (RA). The authors have previously reported that adenosine, acting at specific receptors on inflammatory cells, mediates the antiinflammatory effects of MTX in both in vitro and in vivo models of acute inflammation, but the mechanism by which MTX suppresses the chronic inflammation of arthritis remains controversial. The present study was undertaken to further investigate the means by which adenosine mediates the antiinflammatory effects of MTX. The effects of 2 nonselective adenosine receptor antagonists, theophylline and caffeine, were examined, using the rat adjuvant arthritis model of RA. These agents were given alone and in conjunction with MTX, and arthritis severity was assessed clin., radiol., and histol. Since rodent adenosine A3 receptors are not blocked by theophylline, selective A1, A2A, and A2B receptor antagonists were tested as well. Control animals developed severe arthritis, which was markedly attenuated by weekly treatment with MTX (0.75 mg/kg/wk). Neither theophylline alone nor caffeine alone (each at 10 mg/kg/day) affected the severity of the arthritis, but both agents markedly reversed the effect of MTX as measured by a severity index, hindpaw swelling, and hindpaw ankylosis. Radiog. and histol. analyses confirmed these observations. Neither A1, A2A, nor A2B receptor antagonists affected the capacity of MTX to ameliorate inflammation in adjuvant arthritis. These results provide strong evidence that adenosine mediates the antiinflammatory effects of MTX in this model of RA. Moreover, the findings suggest that abstinence from caffeine, a ubiquitous food additive and medication, may enhance the therapeutic effects of MTX in RA.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1997:472601 CAPLUS

DOCUMENT NUMBER: 127:144925

TITLE: Adenosine A1 receptor promotion of multinucleated giant cell formation by human monocytes A mechanism for methotrexate-induced nodulosis in rheumatoid arthritis

AUTHOR(S): Merrill, Joan T.; Shen, Christine; Schreiber, David; Coffey, Dan; Zakharenko, Olga; Fisher, Robert; Lahita, Robert G.; Salmon, Jane; Cronstein, Bruce N.

CORPORATE SOURCE: St. Luke's/Roosevelt Hospital Center, New York, NY, 10019, USA

SOURCE: Arthritis & Rheumatism (1997), 40(7), 1308-1315  
CODEN: ARHEAW; ISSN: 0004-3591

PUBLISHER: Lippincott-Raven

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To determine why methotrexate (MTX) exacerbates rheumatoid nodules in some patients, despite the effective suppression of synovial inflammation. Phorbol myristate acetate (PMA)-induced differentiation of monocytes into multinucleated giant cells was used as an in vitro model to study the effects of adenosine on nodulosis. MTX at 200-2,000 nM or the adenosine A1 agonist N5-cyclopentyl adenosine (CPA) (10<sup>-12</sup> to 10<sup>-9</sup>M) or the A2 antagonist 3,7-dimethyl-1-propargylxanthine markedly enhanced giant cell formation, whereas the adenosine A1 antagonist 8-cyclopentyl-dipropylxanthine completely reversed these effects. PMA, CPA, and MTX induced adenosine release by cultured monocytes at concns. consistent with those associated with predominantly A1 effects. Furthermore, surface expression of A1 receptors was found to remain unchanged on the differentiating cells throughout the culture period. Agents that inhibit

adenosine A1 receptors might be useful in the treatment of MTX-induced rheumatoid nodulosis, while still potentiating the A2-mediated antiinflammatory effects of MTX on synovitis.

L10 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1997:292734 CAPLUS  
DOCUMENT NUMBER: 127:3470  
TITLE: Purinergic mechanisms in inflammation  
AUTHOR(S): Cronstein, Bruce N.; Bouma, Maarten G.; Becker, Bernhard F.  
CORPORATE SOURCE: Department of Medicine, NYU Medical Center, New York, NY, USA  
SOURCE: Drug Development Research (1997), Volume Date 1996, 39(3/4), 426-435  
CODEN: DDREDK; ISSN: 0272-4391  
PUBLISHER: Wiley-Liss  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review with many refs. Adenosine is now used to treat cardiac arrhythmias and a variety of other potential therapeutic uses for adenosine and its receptor-specific analogs have been suggested. The authors will review here the evidence that adenosine may be useful in the treatment of inflammatory diseases although its potential for promotion of inflammation must be taken into account. The antiinflammatory effects of adenosine and its receptor analogs were first suggested in 1983. Originally shown to diminish neutrophil function via interaction with adenosine A2 receptors, adenosine has a variety of effects on the cells involved in inflammation, which, in general, are antiinflammatory. In this series of reports the authors will discuss the effects of adenosine, acting at its receptors on macrophage/monocytes, and on the synthesis and secretion of the cytokines that orchestrate inflammation. In previous studies, the paradoxical capacity of adenosine to promote the inflammatory functions of neutrophils has been shown to result from A1 receptor occupancy. The authors will discuss here the potential pro-inflammatory role of adenosine, acting at A1 receptors, to enhance the adhesive capacity of vascular endothelium, a critical element in recruiting leukocytes to inflamed sites. Although prior studies have focussed on the potential for adenosine receptor-specific agonists to diminish inflammation it is also possible that endogenously released adenosine plays an antiinflammatory role. The authors will review the evidence that two commonly used and potent antiinflammatory agents, methotrexate and sulfasalazine, diminish inflammation via promotion of adenosine release. The expansion of the potential therapeutic uses of adenosine to include inflammatory diseases may permit the development of novel pharmacol. agents for the treatment of such diseases as rheumatoid arthritis.

REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 14 MEDLINE on STN

ACCESSION NUMBER: 2000191104 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10728760  
TITLE: Reversal of the antiinflammatory effects of methotrexate by the nonselective adenosine receptor antagonists theophylline and caffeine: evidence that the antiinflammatory effects of methotrexate are mediated via multiple adenosine receptors in rat adjuvant arthritis.  
AUTHOR: Montesinos M C; Yap J S; Desai A; Posadas I; McCrary C T; Cronstein B N  
CORPORATE SOURCE: New York University Medical Center, New York, New York 10016, USA.  
CONTRACT NUMBER: AR-41911 (NIAMS)  
GM-56268 (NIGMS)

HL-1972 (NHLBI)

+

SOURCE: Arthritis and rheumatism, (2000 Mar) Vol. 43, No. 3, pp. 656-63.

Journal code: 0370605. ISSN: 0004-3591.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200004

ENTRY DATE: Entered STN: 13 Apr 2000

Last Updated on STN: 13 Apr 2000

Entered Medline: 7 Apr 2000

AB OBJECTIVE: Weekly low-dose methotrexate (MTX) remains the mainstay of second-line therapy for rheumatoid arthritis (RA). We have previously reported that adenosine, acting at specific receptors on inflammatory cells, mediates the antiinflammatory effects of MTX in both in vitro and in vivo models of acute inflammation, but the mechanism by which MTX suppresses the chronic inflammation of arthritis remains controversial. The present study was undertaken to further investigate the means by which adenosine mediates the antiinflammatory effects of MTX. METHODS: The effects of 2 nonselective adenosine receptor antagonists, theophylline and caffeine, were examined, using the rat adjuvant arthritis model of RA. These agents were given alone and in conjunction with MTX, and arthritis severity was assessed clinically, radiologically, and histologically. Since rodent adenosine A3 receptors are not blocked by theophylline, selective A1, A2A, and A2B receptor antagonists were tested as well. RESULTS: Control animals developed severe arthritis, which was markedly attenuated by weekly treatment with MTX (0.75 mg/kg/week). Neither theophylline alone nor caffeine alone (each at 10 mg/kg/day) significantly affected the severity of the arthritis, but both agents markedly reversed the effect of MTX as measured by a severity index, hindpaw swelling, and hindpaw ankylosis. Radiographic and histologic analyses confirmed these observations. Neither A1, A2A, nor A2B receptor antagonists affected the capacity of MTX to ameliorate inflammation in adjuvant arthritis. CONCLUSION: These results provide strong evidence that adenosine mediates the antiinflammatory effects of MTX in this model of RA. Moreover, the findings suggest that abstinence from caffeine, a ubiquitous food additive and medication, may enhance the therapeutic effects of MTX in RA.

L10 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:542261 CAPLUS  
DOCUMENT NUMBER: 145:1031  
TITLE: Methotrexate and an A3 adenosine  
receptor agonist for the treatment of  
inflammation  
INVENTOR(S): Fishman, Pnina; Bar-Yehuda, Sara  
PATENT ASSIGNEE(S): Can-Fite Biopharma Ltd., Israel  
SOURCE: PCT Int. Appl., 35 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006059328	A1	20060608	WO 2005-IL1280	20051130
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
AU 2005310874	A1	20060608	AU 2005-310874	20051130
CA 2586774	A1	20060608	CA 2005-2586774	20051130
EP 1817079	A1	20070815	EP 2005-813139	20051130
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR			
KR 2007100261	A	20071010	KR 2007-714957	20070629
PRIORITY APPLN. INFO.:			US 2004-632198P	P 20041202
			US 2005-657718P	P 20050303
			WO 2005-IL1280	W 20051130
AB	The invention concerns the therapeutic treatment of inflammatory conditions by a combined administration of methotrexate and an agonist of the A3 adenosine receptor. The invention provides methods of therapeutic treatment comprising such a combined administration, pharmaceutical compns. useful in such methods comprising either an and use of either an agonist of the A3 adenosine receptor or methotrexate, as well as use of any of these active agents for preparing such a pharmaceutical composition			
REFERENCE COUNT:	6	THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT		

L10 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

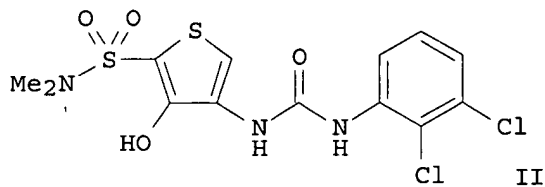
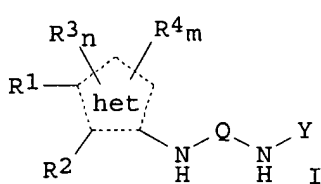
ACCESSION NUMBER: 2005:1259445 CAPLUS  
DOCUMENT NUMBER: 144:22802  
TITLE: Preparation of sulfonylthiophene-substituted ureas and analogs as CXCR1 and CXCR2 chemokine antagonists  
INVENTOR(S): Chao, Jianhua; Taveras, Arthur G.; Aki, Cynthia J.; Lundell, Daniel; Fine, Jay; Priestley, Tony; Reggiani, Angelo  
PATENT ASSIGNEE(S): Schering Corporation, USA  
SOURCE: PCT Int. Appl., 132 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English



FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005113534	A2	20051201	WO 2005-US16507	20050511
WO 2005113534	A3	20061026		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2005245399	A1	20051201	AU 2005-245399	20050511
CA 2565519	A1	20051201	CA 2005-2565519	20050511
US 2006014794	A1	20060119	US 2005-126977	20050511
EP 1745032	A2	20070124	EP 2005-779979	20050511
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU			
CN 1984899	A	20070620	CN 2005-80023232	20050511
JP 2007537272	T	20071220	JP 2007-513317	20050511
KR 2007011475	A	20070124	KR 2006-723571	20061110
US 2007248594	A1	20071025	US 2007-775567	20070710
PRIORITY APPLN. INFO.:			US 2004-570326P	P 20040512
			US 2005-126977	A3 20050511
			WO 2005-US16507	W 20050511
OTHER SOURCE(S):	CASREACT 144:22802; MARPAT 144:22802			
GI				



AB Title compds. I [Y = (un)substituted Ph, pyridinyl, pyrazinyl, etc.; Q = CO, CS, imino, SO<sub>2</sub>; het = thiophene, isothiazole, pyrrole, pyrazole; R<sub>1</sub> = H, halo, alkyl, alkoxy, etc.; R<sub>2</sub> = OH, oxycarbonylamino, amido, etc.; n, m = 0-1; R<sub>3</sub> = halo, CN, CF<sub>3</sub>, etc.; R<sub>4</sub> = aryl, aryl, heteroaryl, etc.] are prepared For instance, N,N-dimethyl-4-amino-3-hydroxythiophene-2-sulfonamide (preparation given) is reacted with 2,3-dichlorophenylisocyanate to give urea II in 73% yield. II and other selected example compds. exhibit a K<sub>i</sub> in the range of 5 nM to 14,800 nM for the CXCR2 receptor. I are useful for the treatment, prevention or amelioration of a CXCR1 or CXCR2 chemokine-mediated disease.

L10 ANSWER 3 OF 14. CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:823681 CAPLUS

DOCUMENT NUMBER: 143:216704

TITLE: Crystalline polymorphs of a CXC-chemokine receptor

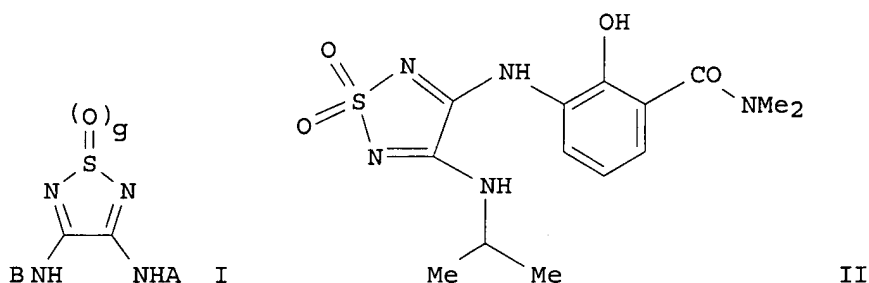
INVENTOR(S): ligand  
Hu, Mengwei; Yu, Younong; Dwyer, Michael; Taveras,  
Arthur G.; Kim-Meade, Agnes; Yin, Jianguo; Fu,  
Xiaoyong; Mcallister, Timothy; Zhang, Shuyi; Klopfer,  
Kevin  
PATENT ASSIGNEE(S): Schering Corporation, USA  
SOURCE: PCT Int. Appl., 65 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005075447	A1	20050818	WO 2005-US3414	20050128
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005210504	A1	20050818	AU 2005-210504	20050128
CA 2554709	A1	20050818	CA 2005-2554709	20050128
US 2005192345	A1	20050901	US 2005-45772	20050128
EP 1723131	A1	20061122	EP 2005-712748	20050128
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU				
CN 1914187	A	20070214	CN 2005-80003507	20050128
BR 2005007329	A	20070703	BR 2005-7329	20050128
JP 2007519751	T	20070719	JP 2006-551613	20050128
MX 2006PA08599	A	20060828	MX 2006-PA8599	20060728
IN 2006CN02800	A	20070608	IN 2006-CN2800	20060728
NO 2006003841	A	20061027	NO 2006-3841	20060829
PRIORITY APPLN. INFO.:			US 2004-540487P	P 20040130
			WO 2005-US3414	W 20050128
AB The present invention relates to 4 distinct crystalline polymorphs of a monohydrate of 2-hydroxy-N,N-dimethyl-3-[[2-[[1-(5-methyl-2-furanyl)propyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]amino]benzamide. These 4 polymorphic forms, herein referred to as Forms I, II, III and IV are active as a CXC-chemokine receptor ligands. The invention is further directed to formulations, methods of treatment, and processes of synthesis of these polymorphic forms.				
REFERENCE COUNT:	3	THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT		
L10 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN				
ACCESSION NUMBER:	2004:333705 CAPLUS			
DOCUMENT NUMBER:	140:357355			
TITLE:	Preparation of diaminothiadiazole dioxides and monoxides as CXC- and CC-chemokine receptor ligands			
INVENTOR(S):	Taveras, Arthur G.; Chao, Jianhua; Biju, Purakkattle J.; Yu, Younong; Fine, Jay S.; Hipkin, William; Aki, Cynthia J.; Merritt, J. Robert; Li, Ge; Baldwin, John J.; Lai, Gaifa; Wu, Minglang; Hecker, Evan A.			
PATENT ASSIGNEE(S):	Pharmacoceia, Inc., USA; Schering Corporation; Pharmacoceia Drug Discovery, Inc.			
SOURCE:	PCT Int. Appl., 540 pp.			

CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004033440	A1	20040422	WO 2003-US31707	20031007
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2501535	A1	20040422	CA 2003-2501535	20031007
AU 2003288922	A1	20040504	AU 2003-288922	20031007
US 2004186142	A1	20040923	US 2003-680393	20031007
EP 1551818	A1	20050713	EP 2003-781311	20031007
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1720240	A	20060111	CN 2003-80105139	20031007
JP 2006508079	T	20060309	JP 2004-543449	20031007
US 2007264230	A1	20071115	US 2007-651128	20070109
PRIORITY APPLN. INFO.:			US 2002-417371P	P 20021009
			US 2003-680393	B1 20031007
			WO 2003-US31707	W 20031007

OTHER SOURCE(S): MARPAT 140:357355  
GI

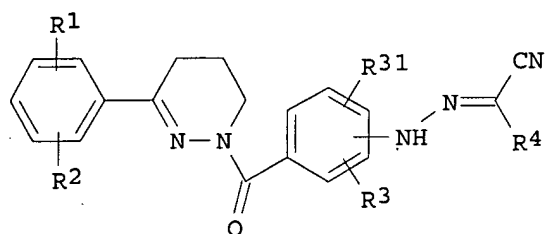


AB Disclosed are diaminothiadiaazole mono- and dioxides (shown as I; e.g. II) and the pharmaceutically acceptable salts and solvates thereof. Examples of substituent A include heteroaryl, aryl, heterocycloalkyl, cycloalkyl, aryl, alkynyl, alkenyl, aminoalkyl, alkyl or amino; examples of substituent B include aryl and heteroaryl; g = 1, 2. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenesis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and cardiac reperfusion injury, acute pain, acute and chronic inflammatory pain, and neuropathic pain using I. Although the methods of preparation are not claimed, hundreds of example preps. and/or characterization data are included. For example, II was prepared in 31% yield from the 4-methoxy analog and isopropylamine in the presence of DIEA in MeOH; the 4-methoxy analog was prepared from the dimethoxy analog and

N,N-dimethyl-3-amino-2-hydroxybenzamide in 99% crude yield. Antagonist activities of some examples of I towards CXCR1, CXCR2 and CCR7 are given.  
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN  
ACCESSION NUMBER: 2003:376641 CAPLUS  
DOCUMENT NUMBER: 138:385438  
TITLE: Preparation of pyridazinylmethanoylphenylhydrazonomalo nitriles as phosphodiesterase IV inhibitors.  
INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael; Beier, Norbert; Schelling, Pierre; Ehring, Thomas  
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany  
SOURCE: PCT Int. Appl., 114 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039548	A1	20030515	WO 2002-EP11351	20021010
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2465746	A1	20030515	CA 2002-2465746	20021010
AU 2002363368	A1	20030519	AU 2002-363368	20021010
AU 2002363368	B2	20071213		
EP 1441730	A1	20040804	EP 2002-802625	20021010
EP 1441730	B1	20060809		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013683	A	20041026	BR 2002-13683	20021010
HU 2004001747	A2	20050128	HU 2004-1747	20021010
CN 1585641	A	20050223	CN 2002-822216	20021010
JP 2005511595	T	20050428	JP 2003-541839	20021010
AT 335486	T	20060915	AT 2002-802625	20021010
ES 2268157	T3	20070316	ES 2002-2802625	20021010
RU 2302412	C2	20070710	RU 2004-117171	20021010
MX 2004PA04263	A	20040708	MX 2004-PA4263	20040504
US 2004261190	A1	20041230	US 2004-494631	20040504
US 7141572	B2	20061128		
ZA 2004004387	A	20060222	ZA 2004-4387	20040603
US 2006270676	A1	20061130	US 2006-497235	20060802
PRIORITY APPLN. INFO.:				A 20011105
				W 20021010
				A1 20040504
OTHER SOURCE(S): MARPAT 138:385438				
GI				



I

AB Title compds. [I; R1, R2 = H, OH, OR5, SR5, SOR5, SO2R5, X; R1R2 = OCH2O, OCH2CH2O; R3, R31 = H, R5, OH, OR5, NH2, NHR5, NHCOR5, X, CO2H, CO2R5, CONH2, etc.; R4 = cyano, tetrazolyl; R5 = (fluoro-substituted) A, cycloalkyl, (CH2)<sub>n</sub>Ar; A = (fluoro- and/or chloro-substituted) alkyl, alkenyl; Ar = Ph; n = 0-2; X = F, Cl, Br, iodo], were prepared Thus, [3-(3,4-diethoxyphenyl)-5,6-dihydro-4H-pyridazine-1-yl]-(3-aminophenyl)methanone (preparation given) was stirred with NaNO<sub>2</sub> in aqueous HCl for

1 h at -2° to 0°; malononitrile in H<sub>2</sub>O was added followed by stirring for 2 h to give a residue which was treated with KOH in MeOH to give 2-[[[3-[1-[3-(3,4-diethoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]methanoyl]phenyl]hydrazono]malononitrile K salt. I were said to give a marked reduction of T cell proliferation. I are claimed for treatment of osteoporosis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, inflammatory processes, allergies, asthma, autoimmune diseases, myocardial diseases, AIDS, etc.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:356269 CAPLUS

DOCUMENT NUMBER: 138:348761

TITLE: Type 4 phosphodiesterase inhibitors and therapeutic uses thereof

INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael

PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany

SOURCE: PCT Int. Appl., 122 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003037349	A1	20030508	WO 2002-EP9596	20020828
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2462525	A1	20030508	CA 2002-2462525	20020828
AU 2002333730	A1	20030512	AU 2002-333730	20020828
EP 1463509	A1	20041006	EP 2002-802281	20020828
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK			
CN 1578665	A	20050209	CN 2002-821711	20020828

HU 2004001984	A2	20050228	HU 2004-1984	20020828
JP 2005515975	T	20050602	JP 2003-539692	20020828
MX 2004PA03668	A	20040722	MX 2004-PA3668	20040419
US 2004259863	A1	20041223	US 2004-494379	20040430
PRIORITY APPLN. INFO.:			EP 2001-125394	A 20011031
			WO 2002-EP9596	W 20020828

OTHER SOURCE(S): MARPAT 138:348761

AB The invention discloses the use of type 4 phosphodiesterase inhibitors (PDE IV inhibitors) to treat diseases, as well as combinations of PDE IV inhibitors with other drugs.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:308358 CAPLUS  
DOCUMENT NUMBER: 140:315066  
TITLE: Methods and reagents using selective serotonin reuptake inhibitors (SSRIs) and corticosteroids for the treatment of diseases and disorders associated with increased levels of proinflammatory cytokines  
INVENTOR(S): Manivasakam, Palaniyandi; Smith, Brendan; Fong, Jason; Auspitz, Benjamin A.; Nichols, M. James; Keith, Curtis; Zimmermann, Grant R.; Brasher, Bradley B.; Sachs, Noah; Chappell, Todd W.; Jost-Price, Edward Roydon  
PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA  
SOURCE: PCT Int. Appl., 104 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 7  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004030618	A2	20040415	WO 2003-US30156	20030924
WO 2004030618	A3	20050407		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2509526	A1	20040415	CA 2003-2509526	20030924
AU 2003299196	A1	20040423	AU 2003-299196	20030924
EP 1553955	A2	20050720	EP 2003-756864	20030924
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
BR 2003014713	A	20050726	BR 2003-14713	20030924
CN 1700921	A	20051123	CN 2003-825315	20030924
JP 2006503905	T	20060202	JP 2005-500317	20030924
MX 2005PA03152	A	20060427	MX 2005-PA3152	20050323
NO 2005001669	A	20050610	NO 2005-1669	20050404
IN 2005CN00669	A	20070810	IN 2005-CN669	20050420
PRIORITY APPLN. INFO.:			US 2002-413040P	P 20020924
			US 2002-417261P	P 20021009
			US 2002-427424P	P 20021119
			US 2002-427526P	P 20021119
			US 2003-464753P	P 20030423
			WO 2003-US30156	W 20030924

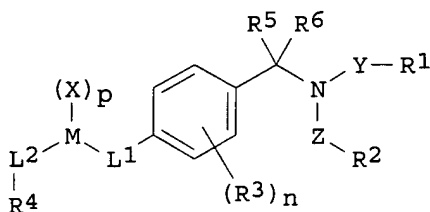
AB The invention discloses a method for treating a patient diagnosed with, or at risk of developing, an immunoinflammatory disorder by administering an SSRI or analog or metabolite thereof and, optionally, a corticosteroid or other compound, to the patient. The invention also features a pharmaceutical composition containing an SSRI or analog or metabolite thereof and a corticosteroid or other compound for the treatment or prevention of an immunoinflammatory disorder.

L17 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:2853 CAPLUS  
DOCUMENT NUMBER: 140:77029  
TITLE: Preparation of heteroarene derivatives as cannabinoid

receptor agonists  
 INVENTOR(S): Kozlowski, Joseph A.; Shankar, Bandarpalle B.; Shih,  
 Neng-yang; Tong, Ling  
 PATENT ASSIGNEE(S): Schering Corporation, USA  
 SOURCE: PCT Int. Appl., 92 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000807	A1	20031231	WO 2003-US19245	20030617
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, US, UZ, VC, VN, YU, ZA, ZM, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2487346	A1	20031231	CA 2003-2487346	20030617
AU 2003243637	A1	20040106	AU 2003-243637	20030617
US 2004044051	A1	20040304	US 2003-464174	20030617
US 7217732	B2	20070515		
EP 1539693	A1	20050615	EP 2003-761108	20030617
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1662496	A	20050831	CN 2003-814441	20030617
JP 2005533809	T	20051110	JP 2004-515897	20030617
MX 2004PA12704	A	20050323	MX 2004-PA12704	20041215
PRIORITY APPLN. INFO.:			US 2002-389788P	P 20020619
OTHER SOURCE(S):			WO 2003-US19245	W 20030617
GI			MARPAT 140:77029	



AB Benzylamine and 1-phenylethylamine compds. containing heteroarene such furan, benzofuran, indole, pyridine, and thiofuran of the formula (I) or pharmaceutically acceptable salts thereof [wherein R1, R2 = H, each (un)substituted alkyl, alkenyl, haloalkyl, NH2, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl; R3 = alkyl, heteroalkyl, aryl, heteroaryl, Br, Cl, F, CF3, OCF2H, OCF3, or alkoxy, wherein R3 can be the same or different and is independently selected when n>1; R4 = (un)substituted H, alkyl, alkenyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl; R5, R6 = H, each (un)substituted alkyl, alkenyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl; R7 = H, each (un)substituted alkyl, alkenyl, haloalkyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl, or two R7 groups can form a ring of 4-7-carbon atoms; L1 = C(R2)2, CO,



[CH(OR2)], SO2, SO, S, O, N(R2), CONH, NHCO, CF2, CH:NOR2, CH(NHOR2); L2 = a covalent bond, CH2, CH(Me), C(Me)2, CH:NOR2, SO2, SO, S, CO, O, N(R2), CONH, NHCO; M = a heteroaryl moiety; n = 0-4; p = 0-5; X = Br, Cl, F, CF3, OH, OCF2H, OCF3, alkoxy, alkyl, cycloalkyl, cycloalkyloxy, heteroalkyl, CON(R7)2, SO2R2, OSO2R2, wherein X is independently selected when p>1; Y = a covalent bond, CH2, SO2, CO; Z = a covalent bond, CH2, SO2, or CO; some provisos are applied] are prepared Disclosed is a method of stimulating cannabinoid CB2 receptors in a patient comprising administering to a patient having CB2 receptors a CB2 receptor stimulating amount of one or more compds. I. Also disclosed is a method of treating cancer, inflammatory diseases, immunomodulatory diseases, or respiratory diseases comprising administering to a patient in need of such treatment one or more compds. I. The said cancer, inflammatory diseases, immunomodulatory diseases or respiratory diseases are one or more diseases selected from the group consisting of cutaneous T cell lymphoma, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, glaucoma, diabetes, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, Crohn's disease, inflammatory bowel disease, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD), and bronchitis.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:833884 CAPLUS

DOCUMENT NUMBER: 139:317425

TITLE: Smac-peptides as therapeutics against cancer and autoimmune diseases by sensitizing for TRAIL- or anticancer drug-induced apoptosis

INVENTOR(S): Debatin, Klaus Michael; Fulda, Simone

PATENT ASSIGNEE(S): Deutsches Krebsforschungszentrum Stiftung des Oeffentlichen Rechts, Germany

SOURCE: Eur. Pat. Appl., 19 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1354952	A1	20031022	EP 2002-8199	20020417
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
EP 1354953	A1	20031022	EP 2002-15499	20020712
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
WO 2003086470	A2	20031023	WO 2003-EP4039	20030417
WO 2003086470	A3	20040506		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003236211	A1	20031027	AU 2003-236211	20030417

EP 1495124	A2	20050112	EP 2003-722503	20030417
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005536457	T	20051202	JP 2003-583486	20030417
US 2005222387	A1	20051006	US 2005-511037	20050119
PRIORITY APPLN. INFO.:			EP 2002-8199	A 20020417

AB The invention is directed to the use of Smac to sensitize different tumors and self-reactive immune cells to various pro-apoptotic stimuli, in that the cells subsequently undergo apoptosis. Therefore, Smac can be used as a compound for the manufacture of a medicament for the treatment of cancer and autoimmune diseases. Sensitization of the cells is achieved either by applying a cell-permeable form of Smac combined with known anticancer agents or by overexpression of the protein. It is an object of the invention to provide a new method in cancer and autoimmune disease therapy by using Smac agonists for apoptosis regulation. Thus, Smac agonists represent novel promising cancer and autoimmune disease therapeutics to potentiate the efficacy of cytotoxic therapies even in resistant tumors and immune cells. In particular, overexpression of full-length Smac protein potentiated TRAIL-induced apoptosis and also markedly increased apoptosis induced by anti-CD95 antibody or cytotoxic drugs in transfected SHEP neuroblastoma cells. The overexpression of Smac is shown to promote apoptosis through antagonizing the inhibition of XIAP of both distal and proximal events in the caspase cascade. The cytosolic Smac, with the deletion of transit peptide for mitochondria (N-terminal 55 AA), bypasses Bcl-2 inhibition in several cell types in response to different pro-apoptotic stimuli. The cell permeable Smac peptide (4 N-terminal IAP-interacting plus 3 addition following residues linked to TAT transduction domain) can facilitate intracellular delivery of Smac peptide and sensitize several resistant cell lines with defects in apoptosis signaling for treatment with TRAIL or doxorubicin. Expression of a cytosolic active form of Smac or cell-permeable Smac peptides bypassed the Bcl-2 block, which prevented the release of Smac from mitochondria, and also sensitized resistant neuroblastoma or melanoma cells and patient-derived primary neuroblastoma cells ex vivo. Thus, Smac agonists represent novel promising cancer therapeutics to potentiate the efficacy of cytotoxic therapies. Smac peptides is shown to enhance the antitumor effect of TRAIL in glioblastoma in mouse glioblastoma model and induce eradication of tumors.

L17 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2008 ACS on STN

DOCUMENT NUMBER: 139:286343

INVENTOR(S) : Krause, James

SOURCE: PCT Int. Appl., 221 pp.

DOCUMENT TYPE: Patent

FAMILY ACC. NUM. COUNT: 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003084524	A1	20031016	WO 2003-US9424	20030327
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,			

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,  
 PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,  
 TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,  
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,  
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,  
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  
 CA 2480082 A1 20031016 CA 2003-2480082 20030327  
 AU 2003220553 A1 20031020 AU 2003-220553 20030327  
 US 2004014782 A1 20040122 US 2003-401113 20030327  
 EP 1490044 A1 20041229 EP 2003-716867 20030327  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK  
 JP 2005530719 T 20051013 JP 2003-581764 20030327  
 PRIORITY APPLN. INFO.: US 2002-368925P P 20020329  
 WO 2003-US9424 W 20030327

OTHER SOURCE(S): MARPAT 139:286343

AB Comps. and methods for treating diseases that are associated with inflammation are provided. Such diseases include arthritis (particularly rheumatoid arthritis) and other autoimmune disorders, asthma, cardio-and cerebrovascular disease, burns, psoriasis, reperfusion injury, and traumatic CNS and spinal cord injury. The comps. generally comprise at least one C5a antagonist and at least one C5a receptor-inactive therapeutic agent. The methods involve co-administration of at least one C5a antagonist and at least one C5a receptor-inactive therapeutic agent to a patient. The C5a antagonist and C5a receptor-inactive therapeutic agent may be present within the same composition, or may be administered sep. to the patient

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1992:120410 CAPLUS

DOCUMENT NUMBER: 116:120410

TITLE: Inhibition of folate-dependent enzymes by non-steroidal anti-inflammatory drugs

AUTHOR(S): Baggott, Joseph E.; Morgan, Sarah L.; Ha, Taisun; Vaughn, William H.; Hine, R. Jean

CORPORATE SOURCE: Dep. Nutr. Sci., Univ. Alabama, Birmingham, AL, 35294, USA

SOURCE: Biochemical Journal (1992), 282(1), 197-202

CODEN: BIJOAK; ISSN: 0306-3275

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Many non-steroidal anti-inflammatory drugs (NSAIDs) (including sulphasalazine, sulindac, indomethacin, naproxen, salicylic acid, ibuprofen, piroxicam and mefenamic acid) were found to be competitive inhibitors (with respect to folate) of avian liver phosphoribosylaminoimidazolecarboxamide formyltransferase (AICAR transformylase, EC 2.1.2.3) and bovine liver dihydrofolate reductase (EC 1.5.1.3). Sphingosine (a potent inhibitor of protein kinase C) at 5-10  $\mu$ M, concns. lower than those that inhibit this enzyme activity, enhanced the aggregation of rabbit platelets induced by low concns. of U46619, platelet-activating factor, thrombin, and arachidonic acid, whereas H-7 and staurosporine, other protein kinase C inhibitors, failed to do so. Of the sphingosine analogs which also inhibit protein kinase C, psychosine and lyso-GM3 did not show such an enhancing effect. In contrast, aspirin and the antipyretic-analgesic drugs acetaminophen and antipyrine were weak inhibitors of these enzymes. Sphingosine promoted both Ins(1,4,5)P3 formation and an increase in the cytoplasmic free Ca<sup>2+</sup> concentration in response to all the agonists used. Structure-activity correlation suggests that an aromatic ring with a side chain containing a

carboxylic acid is a requirement for competitive inhibition of the transformylase. Furthermore, the hydrolytic action of exogenously added phospholipase C (from *Clostridium perfringens*) on platelet membrane phospholipids was dose-dependently enhanced by pretreatment of the platelets with sphingosine. The above-listed NSAIDs also inhibited the folate-coenzyme-mediated biosynthesis of serine from glycine and formate (i.e., the C1 index) by human blood mononuclear cells (BMCs) in expts. where the drug was added to a culture of BMCs. These results imply that sphingosine, at relatively low concns., brings about hyperaggregability of the platelets by the agonists employed, probably owing to enhancement of the phospholipase C activity. Acetaminophen had a weak inhibitory effect on the C1 index. Such an effect appears to be induced by a mechanism independent of protein kinase C inhibition. Consistent with the results obtained in vitro is the observation that the C1 index of BMCs from rheumatoid-arthritis patients treated with drugs which possess little antifolate activity (e.g. acetaminophen) is higher than the C1 index of BMCs from rheumatoid -arthritis patients treated with NSAIDs possessing more potent antifolate activity (e.g. sulindac, sulphasalazine, naproxen and ibuprofen). Sphingosine might act as a pos. modulator for the stimulus-response coupling in the platelets. The mean activity of the transformylase in BMCs taken from healthy humans was 1.98 nmol of product/h per 10<sup>6</sup> cells and the activity was pos. correlated with BMC folate levels. These results are consistent with the hypothesis that (1) the antifolate activity of NSAIDs, and hence cytostatic consequences, are important factors in producing anti-inflammatory activity and (2) aspirin exerts its anti-inflammatory effects after its conversion into salicylic acid, which possesses greater antifolate activity than its parent compound

L17 ANSWER 13 OF 15 MEDLINE on STN  
 ACCESSION NUMBER: 2005233023 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 15868610  
 TITLE: Methotrexate suppresses inflammatory agonist induced interleukin 6 synthesis in osteoblasts.  
 AUTHOR: Yoshida Minoru; Kanno Yosuke; Ishisaki Akira; Tokuda Haruhiko; Hirade Kouseki; Nakajima Keiichi; Katagiri Yoshihiro; Shimizu Katsuji; Kozawa Osamu  
 CORPORATE SOURCE: Department of Pharmacology, Gifu University Graduate School of Medicine, Gifu, Japan.  
 SOURCE: The Journal of rheumatology, (2005 May) Vol. 32, No. 5, pp. 787-95.  
 Journal code: 7501984. ISSN: 0315-162X.  
 PUB. COUNTRY: Canada  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200508  
 ENTRY DATE: Entered STN: 4 May 2005  
 Last Updated on STN: 10 Aug 2005  
 Entered Medline: 9 Aug 2005  
 AB OBJECTIVE: Interleukin 6 (IL-6) is a pleiotropic cytokine that plays a crucial role in the pathogenesis of rheumatoid arthritis (RA). In bone metabolism, it is known that IL-6 is produced and secreted by osteoblasts, and that IL-6 induces osteoclast formation and stimulates bone resorption. Various bone inflammatory agonists such as tumor necrosis factor-alpha (TNF-alpha), IL-1alpha, prostaglandin D2 (PGD2), PGE2, and PGF2alpha, which play important roles in the pathogenesis of RA, induce IL-6 synthesis in osteoblast-like MC3T3-E1 cells. Low dose methotrexate (MTX) is currently used for treatment of patients with RA. We investigated the effect of MTX on IL-6 synthesis induced by these agents in MC3T3-E1 cells. METHODS: Cultured cells were pretreated with various doses of MTX, and then stimulated by

these inflammatory agonists. The IL-6 in the conditioned medium was measured by IL-6 enzyme immunoassay. RESULTS: MTX significantly suppressed IL-6 synthesis stimulated by these agonists in a dose-dependent manner, although MTX alone had no effect on the levels of IL-6. In addition, MTX significantly inhibited the enhancement by IL-17 of TNF-alpha-stimulated IL-6 synthesis. MTX reduced the levels of IL-6 induced by 12-O-tetradecanoylphorbol 13-acetate, a direct activator of protein kinase C (PKC), suggesting that MTX inhibits PKC signals for IL-6 synthesis. CONCLUSION: MTX suppresses IL-6 synthesis stimulated by various inflammatory agonists in osteoblasts.

L17 ANSWER 14 OF 15 MEDLINE on STN  
ACCESSION NUMBER: 2000236276 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10774461  
TITLE: Anti-cytokine therapy for rheumatoid arthritis.  
AUTHOR: Maini R N; Taylor P C  
CORPORATE SOURCE: Kennedy Institute of Rheumatology, London, UK..  
r.maini@ic.ac.uk  
SOURCE: Annual review of medicine, (2000) Vol. 51, pp. 207-29.  
Ref: 78  
Journal code: 2985151R. ISSN: 0066-4219.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
General Review; (REVIEW)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200005  
ENTRY DATE: Entered STN: 6 Jun 2000  
Last Updated on STN: 25 Feb 2003  
Entered Medline: 25 May 2000  
AB Tumor necrosis factor alpha (TNF alpha) and interleukin-1 (IL-1) are important in mediating inflammation in rheumatoid arthritis (RA). Randomized phase II and III clinical trials of anti-TNF reagents (infliximab and etanercept) have demonstrated an acceptable safety profile and marked clinical efficacy in cases of RA that have not responded adequately to conventional therapy. Combination therapy with methotrexate (MTX) appears to be particularly effective in patients whose disease activity persists despite prior disease-modifying antirheumatic drugs (DMARDs) and ongoing MTX monotherapy. DMARD-recalcitrant disease may become the main indication for the use of anti-TNF drugs in patients with RA. Trials of IL-1 receptor antagonist show a relatively modest anti-inflammatory effect and a possible retardation of joint damage. Whether anti-TNF therapy protects joints from structural damage is under investigation. One anti-TNF reagent has already been approved in the United States for the treatment of RA, and other cytokine antagonists or agonists are under development.

L17 ANSWER 15 OF 15 MEDLINE on STN  
ACCESSION NUMBER: 97357081 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9214432  
TITLE: Adenosine A1 receptor promotion of multinucleated giant cell formation by human monocytes: a mechanism for methotrexate-induced nodulosis in rheumatoid arthritis.  
AUTHOR: Merrill J T; Shen C; Schreiber D; Coffey D; Zakharenko O; Fisher R; Lahita R G; Salmon J; Cronstein B N  
CORPORATE SOURCE: St. Luke's/Roosevelt Hospital Center, New York, New York 10019, USA.  
CONTRACT NUMBER: AR-11949 (NIAMS)  
AR/AI-41911 (NIAMS)

K08-AI-01215 (NIAID)  
SOURCE: Arthritis and rheumatism, (1997 Jul) Vol. 40, No. 7, pp. 1308-15.  
Journal code: 0370605. ISSN: 0004-3591.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199707  
ENTRY DATE: Entered STN: 12 Aug 1997  
Last Updated on STN: 29 Jan 1999  
Entered Medline: 29 Jul 1997

AB OBJECTIVE: To determine why methotrexate (MTX) exacerbates rheumatoid nodules in some patients, despite the effective suppression of synovial inflammation. METHODS: Phorbol myristate acetate (PMA)-induced differentiation of monocytes into multinucleated giant cells was used as an in vitro model to study the effects of adenosine on nodulosis. RESULTS: MTX at 200-2,000 nM or the adenosine A1 agonist N5-cyclopentyl adenosine (CPA) ( $10^{-12}$  to  $10^{-9}$  M) or the A2 antagonist 3,7-dimethyl-1-propargylxanthine markedly enhanced giant cell formation, whereas the adenosine A1 antagonist 8-cyclopentyl-dipropylxanthine completely reversed these effects. PMA, CPA, and MTX induced adenosine release by cultured monocytes at concentrations consistent with those associated with predominantly A1 effects. Furthermore, surface expression of A1 receptors was found to remain unchanged on the differentiating cells throughout the culture period. CONCLUSION: Agents that inhibit adenosine A1 receptors might be useful in the treatment of MTX-induced rheumatoid nodulosis, while still potentiating the A2-mediated antiinflammatory effects of MTX on synovitis.

L20 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:1137539 CAPLUS  
DOCUMENT NUMBER: 148:116  
TITLE: The anti-inflammatory effect of A3 adenosine receptor agonists: a novel targeted therapy for rheumatoid arthritis  
AUTHOR(S): Bar-Yehuda, Sara; Silverman, Michael H.; Kerns, William D.; Ochaion, Avivit; Cohen, Shira; Fishman, Pnina  
CORPORATE SOURCE: Can-Fite BioPharma, Petach-Tikva, 49170, Israel  
SOURCE: Expert Opinion on Investigational Drugs (2007), 16(10), 1601-1613  
CODEN: EOIDER; ISSN: 1354-3784  
PUBLISHER: Informa Healthcare  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. Targeting the A3 adenosine receptor (A3AR) to combat inflammation is a new concept based on two findings. First, A3AR is highly expressed in inflammatory cells, whereas low expression is found in normal tissues. This receptor was also found to be overexpressed in peripheral blood mononuclear cells, reflecting receptor status in the remote inflammatory process. Second, A3AR activation with a specific agonist induces de-regulation of the NF- $\kappa$ B signaling pathway in inflammatory cells, as well as initiation of immunomodulatory effects. The A3AR agonist CF-101 (known generically as IB-MECA) induces anti-inflammatory effects in exptl. animal models of collagen- and adjuvant-induced arthritis. Combined therapy with CF-101 and methotrexate in adjuvant-induced arthritis rats yielded an additive anti-inflammatory effect. Methotrexate induced upregulation of A3AR, rendering the inflammatory cells more susceptible to CF-101. In Phase I and in Phase IIa human studies, CF-101 was safe, well tolerated and showed strong evidence of an anti-inflammatory effect in rheumatoid arthritis patients. In peripheral blood mononuclear cells withdrawn from the patients at base line, a statistically significant correlation between A3AR expression level and response to the drug was noted. It is suggested that A3AR may serve as a biol. marker to predict patient response to the drug. Taken together, this information suggests that A3AR agonists may be a new family of orally bioavailable drugs to be developed as potent inhibitors of autoimmune-inflammatory diseases.

REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:1231544 CAPLUS  
DOCUMENT NUMBER: 146:55056  
TITLE: Methotrexate enhances the anti-inflammatory effect of CF101 via up-regulation of the A3 adenosine receptor expression  
AUTHOR(S): Ochaion, A.; Bar-Yehuda, S.; Cohn, S.; Del Valle, L.; Perez-Liz, G.; Madi, L.; Barer, F.; Farbstein, M.; Fishman-Furman, S.; Reitblat, T.; Reitblat, A.; Amital, H.; Levi, Y.; Molad, Y.; Mader, R.; Tishler, M.; Langevitz, P.; Zabutti, A.; Pnina, Fishman  
CORPORATE SOURCE: Can-Fite Biopharma Ltd., Petah-Tikva, 49170, Israel  
SOURCE: Arthritis Research & Therapy (2006), 8(6), No pp. given  
CODEN: ARTRCV; ISSN: 1478-6362  
URL: <http://arthritis-research.com/content/pdf/ar2078.pdf>  
PUBLISHER: BioMed Central Ltd.  
DOCUMENT TYPE: Journal; (online computer file)  
LANGUAGE: English

AB Methotrexate (MTX) exerts an anti-inflammatory effect via its metabolite adenosine which subsequently activates adenosine receptors. The A3 adenosine receptor (A3AR) was found to be highly expressed in inflammatory tissues and peripheral blood mononuclear cells (PBMNC) of adjuvant induced arthritis (AIA) rats. CF101 (IB-MECA), an A3AR agonist, was found earlier to inhibit the clin. and pathol. manifestations of AIA. The aim of the present study was to look at the effect of MTX on A3AR expression level and at the efficacy of the combined treatment of CF101 and MTX in AIA rats. AIA rats were treated with MTX, CF101 or MTX+CF101. A3AR mRNA, protein expression level and exhibition were tested in the paw and PBMNC exts. derived from AIA rats utilizing immunohistochem. staining, RT-PCR and Western blot anal. A3AR level was tested in PBMNC extract derived from chronically treated MTX patients vs. healthy subjects. The effect of CF101, MTX and the combined treatment on A3AR expression level was also tested in PHA stimulated PBMNC from healthy subjects and from MTX treated RA patients. Combined treatment of CF101 and MTX resulted in an additive anti-inflammatory effect in AIA rats. MTX induced A2AAR and A3AR over-expression in the paw cells from the treated animals. Moreover, an increase in A3AR expression level was detected in the PBMNC of MTX treated Rheumatoid arthritis (RA) patients vs. cells from healthy subjects. MTX also increased the protein expression level of PHA stimulated PBMNC from healthy subjects. The increase in A3AR level was counteracted in vitro by adenosine deaminase (ADA) and mimicked in vivo by Dipyrindamole, demonstrating that receptor over-expression was mediated by adenosine. In conclusion, the data presented in this study indicate that MTX induces an increase in A3AR exhibition and expression thereby potentiating the inhibitory effect of CF101, supporting a combined use of these drugs to treat RA.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 4 MEDLINE on STN  
 ACCESSION NUMBER: 2007600480 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 17922624  
 TITLE: The anti-inflammatory effect of A3 adenosine receptor agonists: a novel targeted therapy for rheumatoid arthritis.  
 AUTHOR: Bar-Yehuda Sara; Silverman Michael H; Kerns William D; Ochaion Avivit; Cohen Shira; Fishman Pnina  
 CORPORATE SOURCE: Can-Fite BioPharma, 10 Bareket Street, PO Box 7537, Petach-Tikva 49170, Israel.  
 SOURCE: Expert opinion on investigational drugs, (2007 Oct) Vol. 16, No. 10, pp. 1601-13. Ref: 88  
 Journal code: 9434197. E-ISSN: 1744-7658.  
 PUB. COUNTRY: England; United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200710  
 ENTRY DATE: Entered STN: 10 Oct 2007  
 Last Updated on STN: 16 Oct 2007  
 Entered Medline: 15 Oct 2007

AB Targeting the A(3) adenosine receptor (A(3)AR) to combat inflammation is a new concept based on two findings. First, A(3)AR is highly expressed in inflammatory cells, whereas low expression is found in normal tissues. This receptor was also found to be overexpressed in peripheral blood mononuclear cells, reflecting receptor status in the remote inflammatory process. Second, A(3)AR activation with a specific agonist induces de-regulation of the NF-kappaB signaling pathway in inflammatory cells, as well as initiation of immunomodulatory effects. The A(3)AR agonist CF-101 (known generically as IB-MECA) induces anti-inflammatory effects in experimental animal models of collagen- and adjuvant-induced arthritis. Combined therapy with CF-101 and methotrexate in



adjuvant-induced arthritis rats yielded an additive anti-inflammatory effect. Methotrexate induced upregulation of A(3)AR, rendering the inflammatory cells more susceptible to CF-101. In Phase I and in Phase IIa human studies, CF-101 was safe, well tolerated and showed strong evidence of an anti-inflammatory effect in rheumatoid arthritis patients. In peripheral blood mononuclear cells withdrawn from the patients at base line, a statistically significant correlation between A(3)AR expression level and response to the drug was noted. It is suggested that A(3)AR may serve as a biologic marker to predict patient response to the drug. Taken together, this information suggests that A(3)AR agonists may be a new family of orally bioavailable drugs to be developed as potent inhibitors of autoimmune-inflammatory diseases.

L20 ANSWER 4 OF 4 MEDLINE on STN  
 ACCESSION NUMBER: 2007052342 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 17101059  
 TITLE: Methotrexate enhances the anti-inflammatory effect of CF101 via up-regulation of the A3 adenosine receptor expression.  
 AUTHOR: Ochaion Avivit; Bar-Yehuda Sara; Cohn Shira; Del Valle Luis; Perez-Liz Georginia; Madi Lea; Barer Faina; Farbstein Motti; Fishman-Furman Sari; Reitblat Tatiana; Reitblat Alexander; Amital Howard; Levi Yair; Molad Yair; Mader Reuven; Tishler Moshe; Langevitz Pnina; Zabutti Alexander; Fishman Pnina  
 CORPORATE SOURCE: Can-Fite Biopharma Ltd, 10 Bareket Street, Kiryat-Matalon, Petah-Tikva, 49170, Israel.  
 SOURCE: Arthritis research & therapy, (2006) Vol. 8, No. 6, pp. R169.  
 Journal code: 101154438. E-ISSN: 1478-6362.  
 PUB. COUNTRY: England: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200702  
 ENTRY DATE: Entered STN: 30 Jan 2007  
 Last Updated on STN: 27 Feb 2007  
 Entered Medline: 23 Feb 2007

AB Methotrexate (MTX) exerts an anti-inflammatory effect via its metabolite adenosine, which activates adenosine receptors. The A3 adenosine receptor (A3AR) was found to be highly expressed in inflammatory tissues and peripheral blood mononuclear cells (PBMCs) of rats with adjuvant-induced arthritis (AIA). CF101 (IB-MECA), an A3AR agonist, was previously found to inhibit the clinical and pathological manifestations of AIA. The aim of the present study was to examine the effect of MTX on A3AR expression level and the efficacy of combined treatment with CF101 and MTX in AIA rats. AIA rats were treated with MTX, CF101, or both agents combined. A3AR mRNA, protein expression and exhibition were tested in paw and PBMC extracts from AIA rats utilizing immunohistochemistry staining, RT-PCR and Western blot analysis. A3AR level was tested in PBMC extracts from patients chronically treated with MTX and healthy individuals. The effect of CF101, MTX and combined treatment on A3AR expression level was also tested in PHA-stimulated PBMCs from healthy individuals and from MTX-treated patients with rheumatoid arthritis (RA). Combined treatment with CF101 and MTX resulted in an additive anti-inflammatory effect in AIA rats. MTX induced A2AAR and A3AR over-expression in paw cells from treated animals. Moreover, increased A3AR expression level was detected in PBMCs from MTX-treated RA patients compared with cells from healthy individuals. MTX also increased the protein expression level of PHA-stimulated PBMCs from healthy individuals. The increase in A3AR level was counteracted in vitro by adenosine deaminase and mimicked in vivo by dipyrindamole, demonstrating that receptor over-expression was mediated by adenosine. In conclusion, the data presented here indicate that MTX

induces increased A3AR expression and exhibition, thereby potentiating the inhibitory effect of CF101 and supporting combined use of these drugs to treat RA.

L24 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:453040 CAPLUS  
DOCUMENT NUMBER: 140:417948  
TITLE: Adenosine A3 receptor agonists for the treatment of  
inflammatory arthritis  
INVENTOR(S): Fishman, Pnina  
PATENT ASSIGNEE(S): Can-Fite Biopharma Ltd., Israel  
SOURCE: PCT Int. Appl., 45 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004045627	A1	20040603	WO 2003-IL981	20031119
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2003282359	A1	20040615	AU 2003-282359	20031119
US 2004167094	A1	20040826	US 2003-715823	20031119
US 7141553	B2	20061128		
PRIORITY APPLN. INFO.:			US 2002-427182P P 20021119 WO 2003-IL981 W 20031119	
AB	The invention provides a method for the treatment of inflammatory arthritis, and in particular rheumatoid arthritis, by administering to the subject specific low dosages of N6-(3-iodobenzyl)adenosine-5'-N-methyluronamide (IB-MECA) and 2-chloro-N6-(3-iodobenzyl)adenosine-5'-N-methyluronamide (CL-IB-MECA).			
REFERENCE COUNT:	7	THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT		

L24 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:466173 CAPLUS  
DOCUMENT NUMBER: 139:211534  
TITLE: Adenosine downregulates cytokine-induced expression of intercellular adhesion molecule-1 on rheumatoid synovial fibroblasts independently of adenosine receptor signaling  
AUTHOR(S): Nakazawa, Takashi; Koshihara, Masahiro; Kosaka, Hidekazu; Tsuji, Goh; Nakamachi, Yuji; Saura, Ryuichi; Kurosaka, Masahiro; Tanaka, Yoshiya; Kumagai, Shunichi  
CORPORATE SOURCE: Clinical Pathology and Immunology, Department of Biomedical Informatics, Kobe University Graduate School of Medicine, Kobe, Japan  
SOURCE: Drug Development Research (2003), 58(4), 368-376  
CODEN: DDREDK; ISSN: 0272-4391  
PUBLISHER: Wiley-Liss, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Adhesion of fibroblast-like synoviocytes (FLSs) to T cells through the interaction of lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion mol.-1 (ICAM-1) plays a pivotal role in the pathogenesis of rheumatoid arthritis (RA). The

authors therefore used flow cytometry and quant. polymerase chain reaction (PCR) to examine the effect of adenosine and its derivs. on expression of ICAM-1 induced by TNF- $\alpha$  and interferon- $\gamma$  in primary rheumatoid FLSS (RA-FLSS) and E11 cells, an RA-FLS line. Exposing cells to adenosine (5-500  $\mu$ M) for 24 h in the presence of coformycin, an adenosine deaminase inhibitor, concentration-dependently inhibited cytokine-induced transcription of ICAM-1 mRNA, as well as subsequent surface expression of the protein. Although transcription of all four adenosine receptor isoforms has been detected in FLSS, neither the A1 receptor agonist R-PIA, the A2A receptor agonist CGS21680 nor the A3 agonist CI-IB-MECA had any effect on cytokine-induced ICAM-1 expression. Conversely, A1/A2 receptor antagonist xanthine amine congener and A2A antagonist ZM240385 both failed to suppress the effect of adenosine. Adenosine appears to inhibit cytokine-induced ICAM-1 expression in FLSS independently of adenosine receptor-mediated signaling. By contrast, the effect of adenosine was neutralized by nitrobenzylmercaptapurin, a nucleoside transporter inhibitor, or by ABT702, an adenosine kinase inhibitor. This suggests that adenosine taken up via the nucleoside transporter is phosphorylated by adenosine kinase, and the resultant phospho-adenosine interferes with the ICAM-1 transcription and cell surface expression. Downregulation of T cell-FLS interaction by adenosine may thus represent a novel approach to the treatment of RA.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:833098 CAPLUS  
DOCUMENT NUMBER: 135:370621  
TITLE: The MECA-79 antigen and related methods  
INVENTOR(S): Fukuda, Minoru; Yeh, Jiunn-Chern; Hiraoka, Nobuyoshi  
PATENT ASSIGNEE(S): The Burnham Institute, USA  
SOURCE: PCT Int. Appl., 98 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2001085177	A1	20011115	WO 2001-US15452	20010510
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2004202649	A1	20041014	US 2004-841707	20040506

PRIORITY APPLN. INFO.: US 2000-569320 A2 20000511

AB The present invention provides the structure of the MECA-79 antigen and methods of treating L-selectin-mediated conditions by modulating enzymes that are required for formation of this antigen.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 11 OF 16 MEDLINE on STN

ACCESSION NUMBER: 2007600480 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 17922624  
TITLE: The anti-inflammatory effect of A3 adenosine receptor agonists: a novel targeted therapy for rheumatoid

arthritis.

AUTHOR: Bar-Yehuda Sara; Silverman Michael H; Kerns William D;  
Ochaion Avivit; Cohen Shira; Fishman Pnina

CORPORATE SOURCE: Can-Fite BioPharma, 10 Bareket Street, PO Box 7537,  
Petach-Tikva 49170, Israel.

SOURCE: Expert opinion on investigational drugs, (2007 Oct) Vol.  
16, No. 10, pp. 1601-13. Ref: 88  
Journal code: 9434197. E-ISSN: 1744-7658.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200710

ENTRY DATE: Entered STN: 10 Oct 2007  
Last Updated on STN: 16 Oct 2007  
Entered Medline: 15 Oct 2007

AB Targeting the A(3) adenosine receptor (A(3)AR) to combat inflammation is a new concept based on two findings. First, A(3)AR is highly expressed in inflammatory cells, whereas low expression is found in normal tissues. This receptor was also found to be overexpressed in peripheral blood mononuclear cells, reflecting receptor status in the remote inflammatory process. Second, A(3)AR activation with a specific agonist induces de-regulation of the NF-kappaB signaling pathway in inflammatory cells, as well as initiation of immunomodulatory effects. The A(3)AR agonist CF-101 (known generically as IB-MECA) induces anti-inflammatory effects in experimental animal models of collagen- and adjuvant-induced arthritis. Combined therapy with CF-101 and methotrexate in adjuvant-induced arthritis rats yielded an additive anti-inflammatory effect. Methotrexate induced upregulation of A(3)AR, rendering the inflammatory cells more susceptible to CF-101. In Phase I and in Phase IIa human studies, CF-101 was safe, well tolerated and showed strong evidence of an anti-inflammatory effect in rheumatoid arthritis patients. In peripheral blood mononuclear cells withdrawn from the patients at base line, a statistically significant correlation between A(3)AR expression level and response to the drug was noted. It is suggested that A(3)AR may serve as a biologic marker to predict patient response to the drug. Taken together, this information suggests that A(3)AR agonists may be a new family of orally bioavailable drugs to be developed as potent inhibitors of autoimmune-inflammatory diseases.

L24 ANSWER 12 OF 16 MEDLINE on STN

ACCESSION NUMBER: 2007052342 MEDLINE

DOCUMENT NUMBER: PubMed ID: 17101059

TITLE: Methotrexate enhances the anti-inflammatory effect of CF101 via up-regulation of the A3 adenosine receptor expression.

AUTHOR: Ochaion Avivit; Bar-Yehuda Sara; Cohn Shira; Del Valle Luis; Perez-Liz Georginia; Madi Lea; Barer Faina; Farbstein Motti; Fishman-Furman Sari; Reitblat Tatiana; Réitblat Alexander; Amital Howard; Levi Yair; Molad Yair; Mader Reuven; Tishler Moshe; Langevitz Pnina; Zabutti Alexander; Fishman Pnina

CORPORATE SOURCE: Can-Fite Biopharma Ltd, 10 Bareket Street, Kiryat-Matalon, Petah-Tikva, 49170, Israel.

SOURCE: Arthritis research & therapy, (2006) Vol. 8, No. 6, pp. R169.  
Journal code: 101154438. E-ISSN: 1478-6362.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200702

ENTRY DATE: Entered STN: 30 Jan 2007  
Last Updated on STN: 27 Feb 2007

Entered Medline: 23 Feb 2007

AB Methotrexate (MTX) exerts an anti-inflammatory effect via its metabolite adenosine, which activates adenosine receptors. The A3 adenosine receptor (A3AR) was found to be highly expressed in inflammatory tissues and peripheral blood mononuclear cells (PBMCs) of rats with adjuvant-induced arthritis (AIA). CF101 (IB-MECA), an A3AR agonist, was previously found to inhibit the clinical and pathological manifestations of AIA. The aim of the present study was to examine the effect of MTX on A3AR expression level and the efficacy of combined treatment with CF101 and MTX in AIA rats. AIA rats were treated with MTX, CF101, or both agents combined. A3AR mRNA, protein expression and exhibition were tested in paw and PBMC extracts from AIA rats utilizing immunohistochemistry staining, RT-PCR and Western blot analysis. A3AR level was tested in PBMC extracts from patients chronically treated with MTX and healthy individuals. The effect of CF101, MTX and combined treatment on A3AR expression level was also tested in PHA-stimulated PBMCs from healthy individuals and from MTX-treated patients with rheumatoid arthritis (RA). Combined treatment with CF101 and MTX resulted in an additive anti-inflammatory effect in AIA rats. MTX induced A2AR and A3AR over-expression in paw cells from treated animals. Moreover, increased A3AR expression level was detected in PBMCs from MTX-treated RA patients compared with cells from healthy individuals. MTX also increased the protein expression level of PHA-stimulated PBMCs from healthy individuals. The increase in A3AR level was counteracted in vitro by adenosine deaminase and mimicked in vivo by dipyridamole, demonstrating that receptor over-expression was mediated by adenosine. In conclusion, the data presented here indicate that MTX induces increased A3AR expression and exhibition, thereby potentiating the inhibitory effect of CF101 and supporting combined use of these drugs to treat RA.

L24 ANSWER 13 OF 16 MEDLINE on STN

ACCESSION NUMBER: 2006469972 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 16772045  
TITLE: Induction of PNAd and N-acetylglucosamine  
6-O-sulfotransferases 1 and 2 in mouse collagen-induced  
arthritis.  
AUTHOR: Yang Jiwei; Rosen Steven D; Bendele Philip; Hemmerich  
Stefan  
CORPORATE SOURCE: Thios Pharmaceuticals Inc,, P.O, Box 20010, Oakland, CA  
94620, USA.. jyang@geron.com  
CONTRACT NUMBER: R01-GM57411 (NIGMS)  
R37-GM23547 (NIGMS)  
SOURCE: BMC immunology, (2006) Vol. 7, pp. 12. Electronic  
Publication: 2006-06-13.  
Journal code: 100966980. E-ISSN: 1471-2172.  
PUB. COUNTRY: England: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200609  
ENTRY DATE: Entered STN: 9 Aug 2006  
Last Updated on STN: 26 Sep 2006  
Entered Medline: 25 Sep 2006

AB BACKGROUND: Leukocyte recruitment across blood vessels is fundamental to immune surveillance and inflammation. Lymphocyte homing to peripheral lymph nodes is mediated by the adhesion molecule, L-selectin, which binds to sulfated carbohydrate ligands on high endothelial venules (HEV). These glycoprotein ligands are collectively known as peripheral node addressin (PNAd), as defined by the function-blocking monoclonal antibody known as MECA-79. The sulfation of these ligands depends on the action of two HEV-expressed N-acetylglucosamine 6-O-sulfotransferases: GlcNAc6ST-2 and to a lesser degree GlcNAc6ST-1. Induction of PNAd has also been shown to occur in a number of human inflammatory diseases including

rheumatoid arthritis (RA). RESULTS: In order to identify an animal model suitable for investigating the role of PNAd in chronic inflammation, we examined the expression of PNAd as well as GlcNAc6ST-1 and -2 in collagen-induced arthritis in mice. Here we show that PNAd is expressed in the vasculature of arthritic synovium in mice immunized with collagen but not in the normal synovium of control animals. This de novo expression of PNAd correlates strongly with induction of transcripts for both GlcNAc6ST-1 and GlcNAc6ST-2, as well as the expression of GlcNAc6ST-2 protein. CONCLUSION: Our results demonstrate that PNAd and the sulfotransferases GlcNAc6ST-1 and 2 are induced in mouse collagen-induced arthritis and suggest that PNAd antagonists or inhibitors of the enzymes may have therapeutic benefit in this widely-used mouse model of RA.

L24 ANSWER 14 OF 16 MEDLINE on STN  
 ACCESSION NUMBER: 2005625496 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 16305531  
 TITLE: Purine derivatives as ligands for A3 adenosine receptors.  
 AUTHOR: Joshi Bhalchandra V; Jacobson Kenneth A  
 CORPORATE SOURCE: Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.  
 CONTRACT NUMBER: Z01 DK031117-20 (NIDDK)  
 SOURCE: Current topics in medicinal chemistry, (2005) Vol. 5, No. 13, pp. 1275-95. Ref: 65  
 Journal code: 101119673. ISSN: 1568-0266.  
 PUB. COUNTRY: Netherlands  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, N.I.H., INTRAMURAL)  
 General Review; (REVIEW)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200603  
 ENTRY DATE: Entered STN: 29 Nov 2005  
 Last Updated on STN: 22 Mar 2006  
 Entered Medline: 21 Mar 2006

AB Selective agonists and antagonists for A3 adenosine receptors (ARs) are being explored for the treatment of a variety of disorders, including brain and heart ischemic conditions, cancer, and rheumatoid arthritis. This review covers both the structure activity relationships of nucleoside agonist ligands and selected antagonists acting at this receptor and the routes of synthesis. Highly selective agonists have been designed, using both empirical approaches and a semi-rational approach based on molecular modeling. The prototypical A3 agonists IB-MECA 10 and the more receptor-subtype-selective Cl-IB-MECA 11, both of which have affinity in binding to the receptor of approximately 1 nM, have been used widely as pharmacological probes in the elucidation of the physiological role of this receptor. In addition to the exploration of the effects of structural modification of the adenine and ribose moieties on A3AR affinity, the effects of these structural changes on the intrinsic efficacy have also been studied in a systematic fashion. Key structural features determining A3AR interaction include the N6-benzyl group, 2-position substitution such as halo, substitution of ribose (e.g., the (N)-methanocarba ring system, various 2'- and 3'-substitutions and 4'-thio substitution of oxygen). Conformational studies of the ribose moiety and its equivalents indicate that the ring oxygen is not required and the North (N) ring conformation is preferred in binding to the A3AR. Using these observations, a series of ring constrained (N)-methanocarba 5'-uronamide derivatives was recently reported to be highly selective A3AR agonists, the most notable amongst them was MRS3558 113 having a Ki value in binding to the human A3 receptor of 0.3 nM.

L24 ANSWER 15 OF 16 MEDLINE on STN

ACCESSION NUMBER: 2005197551 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 15752429  
TITLE: A HEV-restricted sulfotransferase is expressed in  
rheumatoid arthritis synovium and is induced by  
lymphotoxin-alpha/beta and TNF-alpha in cultured  
endothelial cells.  
AUTHOR: Pablos Jose L; Santiago Begona; Tsay Durwin; Singer Mark S;  
Palao Guillermo; Galindo Maria; Rosen Steven D  
CORPORATE SOURCE: Servicio de Reumatologia y Unidad de Investigacion,  
Hospital 12 de Octubre, 28041 Madrid, Spain..  
jlpablos@hl2o.es  
CONTRACT NUMBER: R01GM57411 (NIGMS)  
R37GM23547 (NIGMS)  
SOURCE: BMC immunology, (2005) Vol. 6, No. 1, pp. 6. Electronic  
Publication: 2005-03-07.  
Journal code: 100966980. E-ISSN: 1471-2172.  
PUB. COUNTRY: England: United Kingdom  
DOCUMENT TYPE: (COMPARATIVE STUDY)  
Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200603  
ENTRY DATE: Entered STN: 17 Apr 2005  
Last Updated on STN: 1 Apr 2006  
Entered Medline: 31 Mar 2006

AB BACKGROUND: The recruitment of lymphocytes to secondary lymphoid organs  
relies on interactions of circulating cells with high endothelial venules  
(HEV). HEV are exclusive to these organs under physiological conditions,  
but they can develop in chronically-inflamed tissues. The interaction of  
L-selectin on lymphocytes with sulfated glycoprotein ligands on HEV  
results in lymphocyte rolling, which represents the initial step in  
lymphocyte homing. HEV expression of GlcNAc6ST-2 (also known as  
HEC-GlcNAc6ST, GST-3, LSST or CHST4), an HEV-restricted sulfotransferase,  
is essential for the elaboration of L-selectin functional ligands as well  
as a critical epitope recognized by MECA-79 mAb. RESULTS: We  
examined the expression of GlcNAc6ST-2 in relationship to the MECA  
-79 epitope in rheumatoid arthritis (RA) synovial  
vessels. Expression of GlcNAc6ST-2 was specific to RA synovial tissues as  
compared to osteoarthritis synovial tissues and localized to endothelial  
cells of HEV-like vessels and small flat-walled vessels. Double  
MECA-79 and GlcNAc6ST-2 staining showed colocalization of the  
MECA-79 epitope and GlcNAc6ST-2. We further found that both  
TNF-alpha and lymphotoxin-alpha/beta induced GlcNAc6ST-2 mRNA and protein  
in cultured human umbilical vein endothelial cells. CONCLUSION: These  
observations demonstrate that GlcNAc6ST-2 is induced in RA vessels and  
provide potential cytokine pathways for its induction. GlcNAc6ST-2 is a  
novel marker of activated vessels within RA ectopic lymphoid aggregates.  
This enzyme represents a potential therapeutic target for RA.

L24 ANSWER 16 OF 16 MEDLINE on STN

ACCESSION NUMBER: 96194179 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 8620295  
TITLE: Adhesion of rheumatoid lymphocytes to mucosal endothelium:  
the gut revisited.  
AUTHOR: Kadioglu A; Sheldon P  
CORPORATE SOURCE: Department of Microbiology & Immunology, University of  
Leicester, UK.  
SOURCE: British journal of rheumatology, (1996 Mar) Vol. 35, No. 3,  
pp. 218-25.  
Journal code: 8302415. ISSN: 0263-7103.



PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199606  
ENTRY DATE: Entered STN: 27 Jun 1996  
Last Updated on STN: 27 Jun 1996  
Entered Medline: 20 Jun 1996

AB By a study of the adhesion of rheumatoid mononuclear cells, we have sought to clarify the homing properties and origins of cells likely to be involved in the pathogenesis of this disease. The adhesion of mononuclear cells from patients with rheumatoid arthritis (RA) was enumerated by an in vitro adherence assay using frozen sections of endothelium-containing gut lamina propria (EGLP) from porcine small intestine. Preliminary studies verified the involvement of known adhesion molecules by inhibition assays using monoclonal antibodies Meca-367, Mel-14 and Hermes-3. Twenty-five paired samples of peripheral blood (PB) and synovial fluid (SF) were studied, plus six from synovial membrane (SM) and eight from patients with other diseases. There was a significantly greater degree of adherence to EGLP by SF cells than PB (mean adherence  $266 \pm 22$  cells/mm<sup>2</sup>, compared to  $136 \pm 13$  cells/mm<sup>2</sup>, respectively, the majority of which were CD8+ cells;  $P=0.02$ , Mann-Whitney U-test for 25 paired samples). The results of the monoclonal antibody inhibition assays were in keeping with the involvement of homing receptors to gut endothelium in our assay system. Synovial fluid lymphocytes from RA patients exhibited adhesion properties more in keeping with lymphocytes of mucosal than of lymph node origin. Synovial membrane lymphocytes, by contrast, showed poor adherence to endothelium-containing lamina propria. The gut, as an immune lymphoid organ, may thus play a contributory role in this disease, possibly through the pathological seeding of cells into the synovial space.

L24 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:1137539 CAPLUS  
DOCUMENT NUMBER: 148:116  
TITLE: The anti-inflammatory effect of A3 adenosine receptor agonists: a novel targeted therapy for rheumatoid arthritis  
AUTHOR(S): Bar-Yehuda, Sara; Silverman, Michael H.; Kerns, William D.; Ochaion, Avivit; Cohen, Shira; Fishman, Pnina  
CORPORATE SOURCE: Can-Fite BioPharma, Petach-Tikva, 49170, Israel  
SOURCE: Expert Opinion on Investigational Drugs (2007), 16(10), 1601-1613  
CODEN: EOIDER; ISSN: 1354-3784  
PUBLISHER: Informa Healthcare  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. Targeting the A3 adenosine receptor (A3AR) to combat inflammation is a new concept based on two findings. First, A3AR is highly expressed in inflammatory cells, whereas low expression is found in normal tissues. This receptor was also found to be overexpressed in peripheral blood mononuclear cells, reflecting receptor status in the remote inflammatory process. Second, A3AR activation with a specific agonist induces de-regulation of the NF- $\kappa$ B signaling pathway in inflammatory cells, as well as initiation of immunomodulatory effects. The A3AR agonist CF-101 (known generically as IB-MECA) induces anti-inflammatory effects in exptl. animal models of collagen- and adjuvant-induced arthritis. Combined therapy with CF-101 and methotrexate in adjuvant-induced arthritis rats yielded an additive anti-inflammatory effect. Methotrexate induced upregulation of A3AR, rendering the inflammatory cells more susceptible to CF-101. In Phase I and in Phase IIa human studies, CF-101 was safe, well tolerated and showed strong evidence of an anti-inflammatory effect in rheumatoid arthritis patients. In peripheral blood mononuclear cells withdrawn from the patients at base line, a statistically significant correlation between A3AR expression level and response to the drug was noted. It is suggested that A3AR may serve as a biol. marker to predict patient response to the drug. Taken together, this information suggests that A3AR agonists may be a new family of orally bioavailable drugs to be developed as potent inhibitors of autoimmune-inflammatory diseases.

REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:180801 CAPLUS  
DOCUMENT NUMBER: 147:93187  
TITLE: Overexpression of A3 adenosine receptor in peripheral blood mononuclear cells in rheumatoid arthritis: involvement of nuclear factor- $\kappa$ B in mediating receptor level  
AUTHOR(S): Madi, Lea; Cohen, Shira; Ochayin, Avivit; Bar-Yehuda, Sara; Barer, Faina; Fishman, Pnina  
CORPORATE SOURCE: Can-Fite BioPharma Ltd., Petah-Tikva, Israel  
SOURCE: Journal of Rheumatology (2007), 34(1), 20-26  
CODEN: JRHUA9; ISSN: 0315-162X  
PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Objective: A3 adenosine receptor (A3AR) upregulation has been found in cells of synovial tissue and in peripheral blood mononuclear cells (PBMC) of rats with adjuvant-induced arthritis. We investigated A3AR levels in PBMC of patients with rheumatoid arthritis (RA) and in mitogen-activated PBMC from healthy subjects. We examined the role of nuclear factor- $\kappa$ B (NF- $\kappa$ B), a transcription factor present in the A3AR promoter, in

mediating receptor upregulation. Methods: A3AR and NF- $\kappa$ B protein levels were evaluated in PBMC of RA patients (n = 23) and healthy subjects by Western blot. A3AR and NF- $\kappa$ B levels were also analyzed in phytohemagglutinin (PHA) and lipopolysaccharide (LPS)-stimulated PBMC in the presence and absence of antibodies against interleukin 2 (IL-2) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Reverse transcription-polymerase chain reaction was performed in PHA-stimulated PBMC of healthy subjects to determine A3AR expression. Results: A3AR was overexpressed in PBMC of RA patients compared to healthy subjects and was directly correlated to an increase in NF- $\kappa$ B. Similar findings were observed in PHA and LPS-stimulated PBMC from healthy subjects. Antibodies against IL-2 or TNF- $\alpha$  prevented the increase in A3AR and NF- $\kappa$ B expression. Conclusion: Overexpression of A3AR was found in PBMC of RA patients. Receptor upregulation was induced by inflammatory cytokines controlling the expression of the A3AR transcription factor NF- $\kappa$ B.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:1231544 CAPLUS

DOCUMENT NUMBER: 146:55056

TITLE: Methotrexate enhances the anti-inflammatory effect of CF101 via up-regulation of the A3 adenosine receptor expression

AUTHOR(S): Ochaion, A.; Bar-Yehuda, S.; Cohn, S.; Del Valle, L.; Perez-Liz, G.; Madi, L.; Barer, F.; Farbstein, M.; Fishman-Furman, S.; Reitblat, T.; Reitblat, A.; Amital, H.; Levi, Y.; Molad, Y.; Mader, R.; Tishler, M.; Langevitz, P.; Zabutti, A.; Pnina, Fishman

CORPORATE SOURCE: Can-Fite Biopharma Ltd., Petah-Tikva, 49170, Israel

SOURCE: Arthritis Research & Therapy (2006), 8(6), No pp. given

CODEN: ARTRCV; ISSN: 1478-6362

URL: <http://arthritis-research.com/content/pdf/ar2078.pdf>

PUBLISHER: BioMed Central Ltd.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Methotrexate (MTX) exerts an anti-inflammatory effect via its metabolite adenosine which subsequently activates adenosine receptors. The A3 adenosine receptor (A3AR) was found to be highly expressed in inflammatory tissues and peripheral blood mononuclear cells (PBMNC) of adjuvant induced arthritis (AIA) rats. CF101 (IB-MECA), an A3AR agonist, was found earlier to inhibit the clin. and pathol. manifestations of AIA. The aim of the present study was to look at the effect of MTX on A3AR expression level and at the efficacy of the combined treatment of CF101 and MTX in AIA rats. AIA rats were treated with MTX, CF101 or MTX+CF101. A3AR mRNA, protein expression level and exhibition were tested in the paw and PBMNC exts. derived from AIA rats utilizing immunohistochem. staining, RT-PCR and Western blot anal. A3AR level was tested in PBMNC extract derived from chronically treated MTX patients vs. healthy subjects. The effect of CF101, MTX and the combined treatment on A3AR expression level was also tested in PHA stimulated PBMNC from healthy subjects and from MTX treated RA patients. Combined treatment of CF101 and MTX resulted in an additive anti-inflammatory effect in AIA rats. MTX induced A2AAR and A3AR over-expression in the paw cells from the treated animals. Moreover, an increase in A3AR expression level was detected in the PBMNC of MTX treated Rheumatoid arthritis (RA) patients vs. cells from healthy subjects. MTX also increased the protein expression level of PHA stimulated PBMNC from healthy subjects. The increase in A3AR level was counteracted in vitro by adenosine deaminase (ADA) and mimicked in vivo by Dipyrindamole, demonstrating that receptor over-expression was mediated by adenosine. In conclusion, the data presented in this study indicate that MTX induces an increase in A3AR exhibition and expression thereby

potentiating the inhibitory effect of CF101, supporting a combined use of these drugs to treat RA.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:653594 CAPLUS  
DOCUMENT NUMBER: 145:208059  
TITLE: Induction of PNAd and N-acetylglucosamine  
6-O-sulfotransferases 1 and 2 in mouse  
collagen-induced arthritis  
AUTHOR(S): Yang, Jiwei; Rosen, Steven D.; Bendele, Philip;  
Hemmerich, Stefan  
CORPORATE SOURCE: Thios Pharmaceuticals Inc., Oakland, CA, 94620, USA  
SOURCE: BMC Immunology (2006), 7, No pp. given  
CODEN: BIMMCV; ISSN: 1471-2172  
URL: <http://www.biomedcentral.com/content/pdf/1471-2172-7-12.pdf>  
PUBLISHER: BioMed Central Ltd.  
DOCUMENT TYPE: Journal; (online computer file)  
LANGUAGE: English

AB Background Leukocyte recruitment across blood vessels is fundamental to immune surveillance and inflammation. Lymphocyte homing to peripheral lymph nodes is mediated by the adhesion mol., L-selectin, which binds to sulfated carbohydrate ligands on high endothelial venules (HEV). These glycoprotein ligands are collectively known as peripheral node addressin (PNAd), as defined by the function-blocking monoclonal antibody known as MECA-79. The sulfation of these ligands depends on the action of two HEV-expressed N-acetylglucosamine 6-O-sulfotransferases: GlcNAc6ST-2 and to a lesser degree GlcNAc6ST-1. Induction of PNAd has also been shown to occur in a number of human inflammatory diseases including rheumatoid arthritis (RA). Results In order to identify an animal model suitable for investigating the role of PNAd in chronic inflammation, we examined the expression of PNAd as well as GlcNAc6ST-1 and -2 in collagen-induced arthritis in mice. Here we show that PNAd is expressed in the vasculature of arthritic synovium in mice immunized with collagen but not in the normal synovium of control animals. This de novo expression of PNAd correlates strongly with induction of transcripts for both GlcNAc6ST-1 and GlcNAc6ST-2, as well as the expression of GlcNAc6ST-2 protein. Conclusions Our results demonstrate that PNAd and the sulfotransferases GlcNAc6ST-1 and 2 are induced in mouse collagen-induced arthritis and suggest that PNAd antagonists or inhibitors of the enzymes may have therapeutic benefit in this widely-used mouse model of RA.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:1333389 CAPLUS  
DOCUMENT NUMBER: 144:63785  
TITLE: Purine derivatives as ligands for A3 adenosine  
receptors  
AUTHOR(S): Joshi, Bhalchandra V.; Jacobson, Kenneth A.  
CORPORATE SOURCE: Molecular Recognition Section, Laboratory of  
Bioorganic Chemistry, National Institute of Diabetes  
and Digestive and Kidney Diseases, National Institutes  
of Health, Bethesda, MD, 20892, USA  
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United  
Arab Emirates) (2005), 5(13), 1275-1295  
CODEN: CTMCCL; ISSN: 1568-0266  
PUBLISHER: Bentham Science Publishers Ltd.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. Selective agonists and antagonists for A3 adenosine receptors (ARs) are being explored for the treatment of a variety of disorders,

including brain and heart ischemic conditions, cancer, and rheumatoid arthritis. This review covers both the structure activity relationships of nucleoside agonist ligands and selected antagonists acting at this receptor and the routes of synthesis. Highly selective agonists have been designed, using both empirical approaches and a semi-rational approach based on mol. modeling. The prototypical A3 agonists IB-MECA 10 and the more receptor-subtype-selective Cl-IB-MECA 11, both of which have affinity in binding to the receptor of .apprx. 1 nM, have been used widely as pharmacol. probes in the elucidation of the physiol. role of this receptor. In addition to the exploration of the effects of structural modification of the adenine and ribose moieties on A3AR affinity, the effects of these structural changes on the intrinsic efficacy have also been studied in a systematic fashion. Key structural features determining A3AR interaction include the N6-benzyl group, 2-position substitution such as halo, substitution of ribose (e.g., the (N)-methanocarba ring system, various 2'- and 3'-substitutions and 4'-thio substitution of oxygen). Conformational studies of the ribose moiety and its equivalent indicate that the ring oxygen is not required and the North (N) ring conformation is preferred in binding to the A3AR. Using these observations, a series of ring constrained (N)-methanocarba 5'-uronamide derivs. was recently reported to be highly selective A3AR agonists, the most notable amongst them was MRS3558 113 having a Ki value in binding to the human A3 receptor of 0.3 nM.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:298426 CAPLUS

DOCUMENT NUMBER: 142:445850

TITLE: A HEV-restricted sulfotransferase is expressed in rheumatoid arthritis synovium and is induced by lymphotoxin-alpha/beta and TNF-alpha in cultured endothelial cells

AUTHOR(S): Pablos, Jose L.; Santiago, Begona; Tsay, Durwin; Singer, Mark S.; Palao, Guillermo; Galindo, Maria; Rosen, Steven D.

CORPORATE SOURCE: Servicio de Reumatologia y Unidad de Investigacion, Hospital 12 de Octubre, Madrid, 28041, Spain

SOURCE: BMC Immunology (2005), 6, No pp. given  
CODEN: BIMMCV; ISSN: 1471-2172  
URL: <http://www.biomedcentral.com/content/pdf/1471-2172-6-6.pdf>

PUBLISHER: BioMed Central Ltd.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Background: The recruitment of lymphocytes to secondary lymphoid organs relies on interactions of circulating cells with high endothelial venules (HEV). HEV are exclusive to these organs under physiol. conditions, but they can develop in chronically-inflamed tissues. The interaction of L-selectin on lymphocytes with sulfated glycoprotein ligands on HEV results in lymphocyte rolling, which represents the initial step in lymphocyte homing. HEV expression of GlcNAc6ST-2 (also known as HEC-GlcNAc6ST, GST-3, LSST or CHST4), an HEV-restricted sulfotransferase, is essential for the elaboration of L-selectin functional ligands as well as a critical epitope recognized by MECA-79 mAb. Results: We examined the expression of GlcNAc6ST-2 in relationship to the MECA-79 epitope in rheumatoid arthritis (RA) synovial vessels. Expression of GlcNAc6ST-2 was specific to RA synovial tissues as compared to osteoarthritis synovial tissues and localized to endothelial cells of HEV-like vessels and small flat-walled vessels. Double MECA-79 and GlcNAc6ST-2 staining showed colocalization of the MECA-79 epitope and GlcNAc6ST-2. We further found that both TNF- $\alpha$  and lymphotoxin- $\alpha\beta$  induced GlcNAc6ST-2 mRNA and

protein in cultured human umbilical vein endothelial cells. Conclusions: These observations demonstrate that GlcNAc6ST-2 is induced in RA vessels and provide potential cytokine pathways for its induction. GlcNAc6ST-2 is a novel marker of activated vessels within RA ectopic lymphoid aggregates. This enzyme represents a potential therapeutic target for RA.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:288416 CAPLUS

DOCUMENT NUMBER: 142:456557

TITLE: Antiinflammatory effect of A3 adenosine receptor agonists in murine autoimmune arthritis models

AUTHOR(S): Baharav, Ehud; Bar-Yehuda, Sara; Madi, Lea; Silberman, Daniel; Rath-Wolfson, Lea; Halpren, Marisa; Ochaion, Avivit; Weinberger, Abraham; Fishman, Pnina

CORPORATE SOURCE: Can-Fite BioPharma Ltd., Kiryat-Matalon, Israel

SOURCE: Journal of Rheumatology (2005), 32(3), 469-476

CODEN: JRHUA9; ISSN: 0315-162X

PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objective: CF101, an A3 adenosine receptor (A3AR) agonist, is a small orally bioavailable mol. known to suppress in vitro the production of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). We evaluated its therapeutic potential and antiinflammatory effects in 3 murine models of adjuvant induced arthritis (AIA). Methods: The antiinflammatory effect of CF101 was examined in rat AIA, in mouse collagen induced arthritis, and in tropomyosin induced arthritis. The clin. effect of another A3AR agonist, Cl-IB-MECA, was examined in rat AIA. The effect of low dose (10 or 100 mg/kg/day) A3AR agonists administered orally once daily on arthritis severity was assessed clin. and histol. The effect of CF101 on the protein expression level of TNF- $\alpha$  in the synovial tissue, draining lymph nodes, and spleen cells was determined by Western blot. Results: CF101 and Cl-IB-MECA markedly ameliorated the clin. and histol. features of arthritis in the 3 models when administered orally at a low dose of 10 mg/kg body weight in the 3 autoimmune arthritis models. The lower dose of 10 mg/kg of either CF101 or Cl-IB-MECA had better antiinflammatory effect than the higher 100 mg/kg dose. Decreased expression of TNF- $\alpha$  was noted in protein exts. of synovia, draining lymph nodes, and spleen tissues. Conclusion: The results provide evidence that A3AR agonists exert significant antirheumatic effects in different autoimmune arthritis models by suppression of TNF- $\alpha$  production. The beneficial activity of the drugs at the low dose demonstrates that the effect is A3AR mediated.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:235649 CAPLUS

DOCUMENT NUMBER: 133:99286

TITLE: Reversal of the antiinflammatory effects of methotrexate by the nonselective adenosine receptor antagonists theophylline and caffeine: evidence that the antiinflammatory effects of methotrexate are mediated via multiple adenosine receptors in rat adjuvant arthritis

AUTHOR(S): Montesinos, M. Carmen; Yap, Josephine S.; Desai, Avani; Posadas, Inmaculada; McCrary, Christine T.; Cronstein, Bruce N.

CORPORATE SOURCE: New York University Medical Center, New York, NY, 10016, USA

SOURCE: Arthritis & Rheumatism (2000), 43(3), 656-663

CODEN: ARHEAW; ISSN: 0004-3591

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Weekly low-dose methotrexate (MTX) remains the mainstay of 2nd-line therapy for rheumatoid arthritis (RA). The authors have previously reported that adenosine, acting at specific receptors on inflammatory cells, mediates the antiinflammatory effects of MTX in both in vitro and in vivo models of acute inflammation, but the mechanism by which MTX suppresses the chronic inflammation of arthritis remains controversial. The present study was undertaken to further investigate the means by which adenosine mediates the antiinflammatory effects of MTX. The effects of 2 nonselective adenosine receptor antagonists, theophylline and caffeine, were examined, using the rat adjuvant arthritis model of RA. These agents were given alone and in conjunction with MTX, and arthritis severity was assessed clin., radiol., and histol. Since rodent adenosine A3 receptors are not blocked by theophylline, selective A1, A2A, and A2B receptor antagonists were tested as well. Control animals developed severe arthritis, which was markedly attenuated by weekly treatment with MTX (0.75 mg/kg/wk). Neither theophylline alone nor caffeine alone (each at 10 mg/kg/day) affected the severity of the arthritis, but both agents markedly reversed the effect of MTX as measured by a severity index, hindpaw swelling, and hindpaw ankylosis. Radiog. and histol. analyses confirmed these observations. Neither A1, A2A, nor A2B receptor antagonists affected the capacity of MTX to ameliorate inflammation in adjuvant arthritis. These results provide strong evidence that adenosine mediates the antiinflammatory effects of MTX in this model of RA. Moreover, the findings suggest that abstinence from caffeine, a ubiquitous food additive and medication, may enhance the therapeutic effects of MTX in RA.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 2 OF 2 MEDLINE on STN

ACCESSION NUMBER: 2000191104 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10728760

TITLE: Reversal of the antiinflammatory effects of methotrexate by the nonselective adenosine receptor antagonists theophylline and caffeine: evidence that the antiinflammatory effects of methotrexate are mediated via multiple adenosine receptors in rat adjuvant arthritis.

AUTHOR: Montesinos M C; Yap J S; Desai A; Posadas I; McCrary C T; Cronstein B N

CORPORATE SOURCE: New York University Medical Center, New York, New York 10016, USA.

CONTRACT NUMBER: AR-41911 (NIAMS)  
GM-56268 (NIGMS)  
HL-1972 (NHLBI)

SOURCE: +  
 Arthritis and rheumatism, (2000 Mar) Vol. 43, No. 3, pp.  
 656-63.  
 Journal code: 0370605. ISSN: 0004-3591.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 200004  
 ENTRY DATE: Entered STN: 13 Apr 2000  
 Last Updated on STN: 13 Apr 2000  
 Entered Medline: 7 Apr 2000

AB OBJECTIVE: Weekly low-dose methotrexate (MTX) remains the mainstay of second-line therapy for rheumatoid arthritis (RA). We have previously reported that adenosine, acting at specific receptors on inflammatory cells, mediates the antiinflammatory effects of MTX in both in vitro and in vivo models of acute inflammation, but the mechanism by which MTX suppresses the chronic inflammation of arthritis remains controversial. The present study was undertaken to further investigate the means by which adenosine mediates the antiinflammatory effects of MTX. METHODS: The effects of 2 nonselective adenosine receptor antagonists, theophylline and caffeine, were examined, using the rat adjuvant arthritis model of RA. These agents were given alone and in conjunction with MTX, and arthritis severity was assessed clinically, radiologically, and histologically. Since rodent adenosine A<sub>3</sub> receptors are not blocked by theophylline, selective A<sub>1</sub>, A<sub>2A</sub>, and A<sub>2B</sub> receptor antagonists were tested as well. RESULTS: Control animals developed severe arthritis, which was markedly attenuated by weekly treatment with MTX (0.75 mg/kg/week). Neither theophylline alone nor caffeine alone (each at 10 mg/kg/day) significantly affected the severity of the arthritis, but both agents markedly reversed the effect of MTX as measured by a severity index, hindpaw swelling, and hindpaw ankylosis. Radiographic and histologic analyses confirmed these observations. Neither A<sub>1</sub>, A<sub>2A</sub>, nor A<sub>2B</sub> receptor antagonists affected the capacity of MTX to ameliorate inflammation in adjuvant arthritis. CONCLUSION: These results provide strong evidence that adenosine mediates the antiinflammatory effects of MTX in this model of RA. Moreover, the findings suggest that abstinence from caffeine, a ubiquitous food additive and medication, may enhance the therapeutic effects of MTX in RA.



L31 ANSWER 36 OF 46 MEDLINE on STN  
 ACCESSION NUMBER: 93358524 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8353979  
 TITLE: Lack of immunosuppressive effect of low-dose oral  
 methotrexate on lymphocytes in rheumatoid  
 arthritis.  
 AUTHOR: Martinez-Osuna P; Zwolinska J B; Sikes D H; Cory J G;  
 Silveira L H; Jara L J; Espinoza L R  
 CORPORATE SOURCE: Department of Medicine, Louisiana State University Medical  
 Center, New Orleans 70112.  
 SOURCE: Clinical and experimental rheumatology, (1993 May-Jun) Vol.  
 11, No. 3, pp. 249-53.  
 Journal code: 8308521. ISSN: 0392-856X.  
 PUB. COUNTRY: Italy  
 DOCUMENT TYPE: (CLINICAL TRIAL)  
 Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199309  
 ENTRY DATE: Entered STN: 8 Oct 1993  
 Last Updated on STN: 6 Feb 1998  
 Entered Medline: 23 Sep 1993

AB Whether methotrexate (MTX) is effective in rheumatoid  
 arthritis (RA) because of immunosuppressive and/or anti-  
 inflammatory mechanisms of action is controversial. Many lines of  
 investigation point to the latter. We evaluated DNA synthesis in  
 peripheral blood lymphocytes (PBL) from 33 RA patients on  
 oral MTX (7.5-15 mg/wk) and in 30 healthy controls by flow  
 cytometric cell cycle analysis (CCA). DNA synthesis was also evaluated  
 with a thymidilate synthetase activity assay (TSA) (3H-deoxyuridine  
 incorporation) in 12 patients and 21 controls (12 on MTX and  
 NSAID, and 9 healthy subjects). The patients had taken MTX for  
 at least 3 months and were in different stages of clinical activity.  
 There were no significant differences in TSA or in the cell cycle phase  
 distributions (especially the S phase) between treated RA patients  
 and controls. These data suggest that low-dose oral MTX does  
 not inhibit DNA synthesis and therefore does not have an immunosuppressive  
 effect on lymphocytes from patients with RA.

L31 ANSWER 37 OF 46 MEDLINE on STN  
 ACCESSION NUMBER: 92295014 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 1604414  
 TITLE: The treatment of rheumatoid arthritis  
 with low dose pulse methotrexate--comparative study with  
 other disease modifying antirheumatic drugs.  
 AUTHOR: Murayama T; Ubukata A; Nakazaki S  
 CORPORATE SOURCE: Center of Rheumatology and Collagen Diseases, Kanazawa  
 Rehabilitation Hospital.  
 SOURCE: Ryumachi. [Rheumatism], (1992 Feb) Vol. 32, No. 1, pp.  
 3-11.  
 Journal code: 0153217. ISSN: 0300-9157.  
 PUB. COUNTRY: Japan  
 DOCUMENT TYPE: (CLINICAL TRIAL)  
 (COMPARATIVE STUDY)  
 (CONTROLLED CLINICAL TRIAL)  
 (ENGLISH ABSTRACT)  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: Japanese  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199207  
 ENTRY DATE: Entered STN: 24 Jul 1992  
 Last Updated on STN: 29 Jan 1996

Entered Medline: 14 Jul 1992

AB Low dose pulse methotrexate (MTX, 5-7.5mg/week) was administered to fifty one patients with severe and active rheumatoid arthritis (RA) who did not respond to the various disease modifying antirheumatic drugs (DMARDs). The follow-up period ranged from 2 to 30 months. As to efficacy rate and probability of patients continuing therapy, the results of MTX were compared with those of the other DMARDs (131 cases of bucillamine (BU), 163 of D-penicillamine (DP), 98 of salazopyrin (SASP), 126 of auranofin (AF), 55 of lobenzarit (CCA)). The patients treated with MTX showed remarkable improvement within 1 or 2 months in Lansbury's index items, CRP, immunoglobulin levels and rheumatoid factor values. But OKT4/8 ratio remained unchanged throughout the study period. As to the adverse reactions due to MTX an elevation of serum transaminase occurred most frequently (41.2%). MTX treatment was, however, tolerable to the most cases with its transient discontinuance or its dose reduction. The efficacy rate of MTX (71.4%) was the best among above mentioned DMARDs at the end of 6 months treatment. After treatment of 24 months, the probability of still taking MTX (70.1%) proved to be about the same with that of DP and better than that of BU, SASP, AF and CCA. In conclusion low dose pulse MTX turned out to be effective in the treatment of severe and active rheumatoid arthritis.

L31 ANSWER 38 OF 46 MEDLINE on STN

ACCESSION NUMBER: 92195359 MEDLINE

DOCUMENT NUMBER: PubMed ID: 1549149

TITLE: Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group.

AUTHOR: Giannini E H; Brewer E J; Kuzmina N; Shaikov A; Maximov A; Vorontsov I; Fink C W; Newman A J; Cassidy J T; Zemel L S

CORPORATE SOURCE: Department of Pediatrics, University of Cincinnati College of Medicine, OH.

CONTRACT NUMBER: FD-R-000032 (FDA)

SOURCE: The New England journal of medicine, (1992 Apr 16) Vol. 326, No. 16, pp. 1043-9.

Journal code: 0255562. ISSN: 0028-4793.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

(MULTICENTER STUDY)

(RANDOMIZED CONTROLLED TRIAL)

(RESEARCH SUPPORT, NON-U.S. GOV'T)

(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199204

ENTRY DATE: Entered STN: 9 May 1992

Last Updated on STN: 3 Feb 1997

Entered Medline: 21 Apr 1992

AB BACKGROUND. The antimetabolite methotrexate has been shown in placebo-controlled trials to be effective in adults with rheumatoid arthritis. Methotrexate may also be effective in children with resistant juvenile rheumatoid arthritis, but the supporting data are from uncontrolled trials. METHODS. Centers in the United States and the Soviet Union participated in this randomized, controlled, double-blind trial designed to evaluate the effectiveness and safety of orally administered methotrexate. Patients received one of the following treatments each week for six months: 10 mg of methotrexate per square meter of body-surface area (low dose), 5 mg of methotrexate per square meter (very low dose), or placebo. The use of prednisone (less than or equal to 10 mg

per day) and two nonsteroidal antiinflammatory drugs was also allowed.

**RESULTS.** The 127 children (mean age, 10.1 years) had a mean duration of disease of 5.1 years; 114 qualified for the analysis of efficacy. According to a composite index of several response variables, 63 percent of the children who received low-dose methotrexate improved, as compared with 32 percent of those in the very-low-dose group and 36 percent of those in the placebo group ( $P = 0.013$ ). As compared with the placebo group, the low-dose group also had significantly larger mean reductions from base line in the number of joints with pain on motion (-11.0 vs. -7.1), the pain-severity score (-19 vs. -11.5), the number of joints with limited motion (-5.4 vs. -0.7), and the erythrocyte sedimentation rate (-19.0 vs. -6 mm per hour). In the methotrexate groups only three children had the drug discontinued because of mild-to-moderate side effects; none had severe toxicity.

**CONCLUSIONS.** Methotrexate given weekly in low doses is an effective treatment for children with resistant juvenile rheumatoid arthritis, and at least in the short term this regimen is safe.

L31 ANSWER 39 OF 46 MEDLINE on STN  
 ACCESSION NUMBER: 91332265 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 1678395  
 TITLE: Low-dose weekly methotrexate for unusual neutrophilic vascular reactions: cutaneous polyarteritis nodosa and Behcet's disease.  
 AUTHOR: Jorizzo J L; White W L; Wise C M; Zanolli M D; Sherertz E F  
 CORPORATE SOURCE: Department of Dermatology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC 27103.  
 SOURCE: Journal of the American Academy of Dermatology, (1991 Jun) Vol. 24, No. 6 Pt 1, pp. 973-8. Journal code: 7907132. ISSN: 0190-9622.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: (CASE REPORTS)  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199109  
 ENTRY DATE: Entered STN: 6 Oct 1991  
 Last Updated on STN: 6 Feb 1995  
 Entered Medline: 19 Sep 1991

AB Low-dose weekly methotrexate therapy has been used to treat patients with psoriasis for more than 20 years. This regimen has also been used to treat rheumatoid arthritis, inflammatory bowel disease, primary sclerosing cholangitis, and corticosteroid-dependent asthma. We report two patients with Behcet's disease with cutaneous neutrophilic vascular reactions and three with cutaneous polyarteritis nodosa who responded dramatically to low-dose weekly methotrexate therapy.

L31 ANSWER 40 OF 46 MEDLINE on STN  
 ACCESSION NUMBER: 91315630 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 1859490  
 TITLE: Methotrexate versus azathioprine in the treatment of rheumatoid arthritis. A forty-eight-week randomized, double-blind trial.  
 AUTHOR: Jeurissen M E; Boerbooms A M; van de Putte L B; Doesburg W H; Mulder J; Rasker J J; Kruijsen M W; Haverman J F; van Beusekom H J; Muller W H; +  
 CORPORATE SOURCE: Department of Rheumatology, University Hospital Nijmegen, The Netherlands.  
 SOURCE: Arthritis and rheumatism, (1991 Aug) Vol. 34, No. 8, pp. 961-72. Journal code: 0370605. ISSN: 0004-3591.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: (CLINICAL TRIAL)

(COMPARATIVE STUDY)  
Journal; Article; (JOURNAL ARTICLE)  
(RANDOMIZED CONTROLLED TRIAL)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199108  
ENTRY DATE: Entered STN: 13 Sep 1991  
Last Updated on STN: 13 Sep 1991  
Entered Medline: 29 Aug 1991

AB We conducted a double-blind, randomized trial comparing azathioprine (AZA) and methotrexate (MTX) in the treatment of patients with rheumatoid arthritis in whom parenteral gold and/or D-penicillamine treatment had been unsuccessful. Patients were randomly assigned to receive either AZA (100 mg daily) or oral MTX (7.5 mg weekly). After 8 weeks, the dosage was increased depending on the clinical improvement. Sixty-four patients were followed up for 48 weeks (33 AZA, 31 MTX). Comparison of values at week 24 with baseline values revealed significant improvement in 12 of 13 disease variables in the MTX group and in 6 of 13 in the AZA group. Comparison between the 2 treatment groups at 24 weeks, by area-under-the-curve analysis, showed significantly more improvement in the MTX group in terms of the swollen joint count, pain score, erythrocyte sedimentation rate, C-reactive protein level, hemoglobin level, thrombocyte level, and disease activity score. A significant overall clinical improvement (disease activity score) was found in 7 of 20 patients treated with AZA and 18 of 30 patients treated with MTX after 24 weeks of therapy, and in 6 of 12 AZA-treated patients and 19 of 25 MTX-treated patients after 48 weeks. The number of withdrawals due to side effects was significantly higher in the AZA group. After 48 weeks, only 12 patients from the AZA group (36%), but 25 from the MTX group (81%), were still using the initial drug. These results demonstrate MTX to be superior to AZA in the treatment of rheumatoid arthritis, with a more rapid clinical improvement which is sustained after 1 year, accompanied by a lower rate of serious adverse reactions.

L31 ANSWER 41 OF 46 MEDLINE on STN  
ACCESSION NUMBER: 91229262 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 2029111  
TITLE: Influence of methotrexate and azathioprine on radiologic progression in rheumatoid arthritis. A randomized, double-blind study.  
AUTHOR: Jeurissen M E; Boerbooms A M; van de Putte L B; Doesburg W H; Lemmens A M  
CORPORATE SOURCE: Department of Rheumatology, University Hospital Nijmegen, The Netherlands.  
SOURCE: Annals of internal medicine, (1991 Jun 15) Vol. 114, No. 12, pp. 999-1004.  
Journal code: 0372351. ISSN: 0003-4819.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
(COMPARATIVE STUDY)  
Journal; Article; (JOURNAL ARTICLE)  
(RANDOMIZED CONTROLLED TRIAL)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199106  
ENTRY DATE: Entered STN: 30 Jun 1991  
Last Updated on STN: 30 Jun 1991  
Entered Medline: 11 Jun 1991

AB OBJECTIVE: To compare the effects of azathioprine and methotrexate on progression of radiologic damage in patients with

rheumatoid arthritis. DESIGN: Double-blind, randomized 48-week trial. PATIENTS: Sixty-four patients with active rheumatoid arthritis who either have not responded to or who have reacted with side effects to at least parenteral gold and D-penicillamine. INTERVENTIONS: Either azathioprine, 100 mg daily, or methotrexate, 7.5 mg weekly, was administered orally. Depending on the clinical effect after 8 weeks, the dosage was increased to either azathioprine, 150 mg, or methotrexate, 15 mg. The dosages for nonsteroidal anti-inflammatory drugs and prednisone were held stable. MEASUREMENTS: Clinical and laboratory assessments were done by the same physician every 4 weeks for the first 24 weeks and every 8 weeks thereafter. Radiographs of hands, wrists, and feet obtained at baseline and after 24 and 48 weeks were scored by one rheumatologist blinded to medication and clinical findings. MAIN RESULTS: Initial radiologic scores were comparable in both groups and correlated with disease duration ( $r = 0.38$ ). An intention-to-treat analysis after 24 and 48 weeks showed significantly fewer new erosions in the methotrexate group compared with the azathioprine group (difference, 2.0 [95% CI, 0.2 to 3.9] and 3.5 [CI, 1.3 to 5.8], respectively). The change in total joint score was also significantly less pronounced in the methotrexate group compared with the azathioprine group after 24 weeks (difference, 2.8 [CI, 0.2 to 5.2]) and after 48 weeks (difference, 3.9 [CI, 0.3 to 7.4]). Radiologic stabilization after 48 weeks was present in 10% of the azathioprine group compared with 29% of the methotrexate group. CONCLUSIONS: Patients with rheumatoid arthritis treated with low-dose methotrexate showed significantly less radiologic progression than patients treated with azathioprine. This result suggests that methotrexate therapy is clinically superior in these patients.

L31 ANSWER 42 OF 46 MEDLINE on STN  
 ACCESSION NUMBER: 91011902 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 2213397  
 TITLE: Safety and efficacy of methotrexate therapy for juvenile rheumatoid arthritis.  
 AUTHOR: Rose C D; Singen B H; Eichenfield A H; Goldsmith D P; Athreya B H  
 CORPORATE SOURCE: Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia.  
 SOURCE: The Journal of pediatrics, (1990 Oct) Vol. 117, No. 4, pp. 653-9.  
 Journal code: 0375410. ISSN: 0022-3476.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 199011  
 ENTRY DATE: Entered STN: 17 Jan 1991  
 Last Updated on STN: 15 Jan 2003  
 Entered Medline: 5 Nov 1990

AB Twenty-nine children with juvenile rheumatoid arthritis were studied to determine the safety and efficacy of methotrexate therapy. The initial dose of methotrexate averaged 7.1 mg/m<sup>2</sup>/wk and was given as a single, oral weekly dose or as three divided doses, each separated by 12 hours. Current antiinflammatory medications were continued; 25 of 29 children had had lack of efficacy, and 8 of 29 had toxic effects, with one or more prior drugs such as intramuscularly or orally administered gold, hydroxychloroquine, or D-penicillamine. Intolerable corticosteroid dependency or toxic effects were present in 18 of 29 cases. Methotrexate-treated patients were examined monthly; minimum treatment duration required to assess efficacy and toxicity was 6 months. The range of treatment duration was 8 to 39 months (mean 18.5 months). Efficacy was assessed by comparing pretreatment versus posttreatment fever and rash, swollen-joint counts, articular

indexes, duration of morning stiffness, functional class, hemoglobin levels, and platelet counts. Treatment with methotrexate effectively controlled fever and rash in 83% of children with systemic juvenile rheumatoid arthritis, reduced morning stiffness by 63%, eliminated recalcitrant joint restriction in 48%, and reduced numbers of swollen joints and swelling indexes by 46% and 52%, respectively. No significant toxic effects were observed. Juvenile rheumatoid arthritis of long duration, or with major erosions, was more likely to be refractory to methotrexate therapy. We recommend earlier consideration of methotrexate in place of other slow-acting antirheumatic drugs for juvenile rheumatoid arthritis not responding well to usual therapy. Future studies should address potential methotrexate toxic effects in the lungs and reproductive system, as well as outcome after discontinuation of methotrexate treatment.

L31 ANSWER 43 OF 46 MEDLINE on STN  
 ACCESSION NUMBER: 90271202 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 2348423  
 TITLE: Treatment of rheumatoid arthritis with higher dose intravenous methotrexate.  
 AUTHOR: Gabriel S; Creagan E; O'Fallon W M; Jaquith J; Bunch T  
 CORPORATE SOURCE: Mayo Clinic, Department of Rheumatology, Rochester, MN 55905.  
 SOURCE: The Journal of rheumatology, (1990 Apr) Vol. 17, No. 4, pp. 460-5.  
 Journal code: 7501984. ISSN: 0315-162X.  
 PUB. COUNTRY: Canada  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199007  
 ENTRY DATE: Entered STN: 10 Aug 1990  
 Last Updated on STN: 10 Aug 1990  
 Entered Medline: 11 Jul 1990

AB A pilot study evaluated intravenous methotrexate (MTX) (initial dose 40 mg/m<sup>2</sup>; final dose, 26 mg/m<sup>2</sup>), weekly for 12 weeks in 10 patients with rheumatoid arthritis who failed oral MTX. Statistically significant differences were noted for all the response variables examined: joint count (p = 0.0017), morning stiffness (p = 0.014), global assessment (patient, p = 0.0032, physician, p = 0.029), Arthritis Impact Measurement Scale (p = 0.0004), erythrocyte sedimentation rate (p = 0.012), grip strength (right p = 0.044, left p = 0.011). All 7 patients who completed the 12-week treatment period fulfilled the predetermined criteria for response. Intravenous MTX at these doses has potential efficacy in this patient group.

L31 ANSWER 44 OF 46 MEDLINE on STN  
 ACCESSION NUMBER: 89068601 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 3199396  
 TITLE: Methotrexate kinetics in rheumatoid arthritis: is there an interaction with nonsteroidal antiinflammatory drugs?.  
 AUTHOR: Ahern M; Booth J; Loxton A; McCarthy P; Meffin P; Kevat S  
 CORPORATE SOURCE: Department of Medicine, Flinders University of South Australia.  
 SOURCE: The Journal of rheumatology, (1988 Sep) Vol. 15, No. 9, pp. 1356-60.  
 Journal code: 7501984. ISSN: 0315-162X.  
 PUB. COUNTRY: Canada  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals

ENTRY MONTH: 198901  
ENTRY DATE: Entered STN: 8 Mar 1990  
Last Updated on STN: 8 Mar 1990  
Entered Medline: 18 Jan 1989

AB Pharmacokinetic drug interaction between methotrexate (MTX) and nonsteroidal anti-inflammatory drugs (NSAID) has been implicated in several case reports of MTX related toxicity. We therefore studied the kinetics of low dose (15 mg) oral MTX with and without concomitant NSAID therapy after preliminary determination of the systemic bioavailability of commercial tablets. Fourteen patients with rheumatoid arthritis, age range 44-77 years, participated in paired kinetic studies performed 1-4 weeks apart. The Abbott TDx fluorescence polarization immunoassay was used to measure serum levels and urinary excretion of MTX over 72 h after a single dose. The mean systemic bioavailability was 73% for the 15 mg oral dose. Area under the serum concentration versus time curve for a 50 mg oral dose was 1.1-2.7 times that of the 15 mg oral dose indicating dose dependent absorption. Mean kinetic variables after oral MTX did not differ significantly with and without NSAID therapy despite apparent interactions in individual patients. Renal clearance of MTX correlated with creatinine clearance ( $r = 0.8$ ,  $p$  less than 0.01).

L31 ANSWER 45 OF 46 MEDLINE on STN  
ACCESSION NUMBER: 87297046 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 3304050  
TITLE: Methotrexate in rheumatoid arthritis.  
Indications, contraindications, efficacy, and safety.  
AUTHOR: Tugwell P; Bennett K; Gent M  
SOURCE: Annals of internal medicine, (1987 Sep) Vol. 107, No. 3,  
pp. 358-66. Ref: 54  
Journal code: 0372351. ISSN: 0003-4819.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 198709  
ENTRY DATE: Entered STN: 5 Mar 1990  
Last Updated on STN: 5 Mar 1990  
Entered Medline: 24 Sep 1987

AB Evidence on the safety and efficacy of methotrexate as a second- or third-line agent for treating patients with rheumatoid arthritis is reviewed. Four placebo-controlled clinical trials have documented short-term benefit from methotrexate; although true remission is rare, patients receiving methotrexate showed a 26% (95% confidence interval [CI], 17% to 35%) greater improvement in their inflamed joint count and a 39% (95% CI, 26% to 51.5%) greater improvement in pain than did controls receiving nonsteroidal anti-inflammatory agents with or without prednisone. With respect to long-term benefit, improvement usually occurs within 1 month, reaching a maximum at 6 and then leveling off for the duration of treatment; in some patients, the benefit may wane after an initial satisfactory response in the first 4 to 6 months. In one third of those given methotrexate, treatment had to be discontinued because of adverse effects, less than 1% of which were life threatening. Careful baseline and follow-up monitoring is recommended until more data on the safety of methotrexate are available.

L31 ANSWER 46 OF 46 MEDLINE on STN  
ACCESSION NUMBER: 87156852 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 3548731  
TITLE: Mast cell numbers in rheumatoid synovial tissues.  
Correlations with quantitative measures of lymphocytic

infiltration and modulation by antiinflammatory therapy.  
AUTHOR: Malone D G; Wilder R L; Saavedra-Delgado A M; Metcalfe D D  
SOURCE: Arthritis and rheumatism, (1987 Feb) Vol. 30, No. 2, pp.  
130-7.  
Journal code: 0370605. ISSN: 0004-3591.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (COMPARATIVE STUDY)  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 198704  
ENTRY DATE: Entered STN: 3 Mar 1990  
Last Updated on STN: 3 Mar 1990  
Entered Medline: 6 Apr 1987

AB Synovial biopsy specimens from 20 patients with rheumatoid arthritis were subjected to quantitative analysis for several parameters of inflammation and for enumeration of synovial tissue mast cells. Strong positive correlations were found between numbers of mast cells per cubic millimeter of synovial tissue and the following synovial tissue parameters: inflammatory index (a quantification of lymphocytic infiltration), Leu-3a grade (T helper/inducer lymphocytes), Leu-1 grade (T lymphocyte), and plasma cell grade. A strong negative correlation was found between the synovial mast cell count and the extent of sublining layer fibrin deposition. Correlations between synovial mast cell count and Leu-2a grade, ratio of Leu-3a grade:Leu-2a grade, OKM1 grade, HLA-DR grade, and lining layer thickness grade did not reach statistical significance. In addition, we obtained synovial specimens from 6 of the patients both before and after long-term therapy with oral methotrexate and from 3 of the patients before, and 1 week after, an intraarticular injection of steroid. The 3 patients who had an intraarticular steroid injection showed a 67-96% decrease in the number of synovial tissue mast cells; there was no significant change in the number of synovial mast cells in the tissues of the 6 patients who received oral methotrexate. These observations are the first documentation of a quantitative relationship between the number of mast cells and the number and phenotypic profile of infiltrating lymphocytes in an inflamed tissue, which in this case, is human synovium. Our findings suggest that mast cells are involved in the pathologic interactions in rheumatoid arthritis and might play a role in the early phases of exacerbations of disease activity.



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(FILE 'HOME' ENTERED AT 14:55:13 ON 20 JAN 2008)

FILE 'REGISTRY' ENTERED AT 14:57:36 ON 20 JAN 2008  
E METHOTREXATE/CN

L1 1 S E3

FILE 'CAPLUS, MEDLINE' ENTERED AT 14:58:54 ON 20 JAN 2008

L2 40819 S L1  
L3 0 S L2 AND ?UROMAMIDE?  
L4 0 S L2 AND ?UROAMIDE?  
L5 2 S L2 AND ?URONAMIDE?  
L6 40817 S L2 NOT L5  
L7 3740 S L6 AND RHEUMATOID ARTHRITIS  
L8 2 S L7 AND A3AR  
L9 3738 S L7 NOT L8  
L10 14 S L9 AND ADENOSINE RECEPTOR?  
L11 187265 S HIS  
L12 3724 S L9 NOT L10  
L13 2583 S L12 AND PATIENT?  
L14 0 S L13 AND ?MECA  
L15 0 S L12 AND ?MECA  
L16 805 S L13 AND INFLAMM?  
L17 15 S L16 AND AGONIST?  
L18 0 S METHOTREXATE/TI (P) ?MECA/CN  
L19 0 S METHOTREXATE/TI (P) ?MECA/TI  
L20 4 S METHOTREXATE (P) ?MECA (P) RHEUMATOID ARTHRITIS  
L21 4 S METHOTREXATE (P) ?MECA (P) ARTHRITIS  
L22 0 S L20 NOT L21  
L23 109 S L16 AND ORAL?  
L24 16 S ?MECA (P) RHEUMATOID ARTHRITIS  
L25 0 S L23 AND ADENOSINE A3 RECEPTOR?  
L26 0 S L23 AND A3 RECEPTOR?  
L27 2 S L9 AND ADENOSINE A3 RECEPTOR?  
L28 3736 S L9 NOT L27  
L29 0 S L28 AND A3 RECEPTOR?  
L30 0 S L23 AND DOSEGE?  
L31 46 S L23 AND DOSAGE?